THE TREATMENT

OF

TUBERCULOUS MENINGITIS

An Analysis of Results of Treatment in 52 Cases and a Review of Modern Therapy

by

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"Even the most assiduous workman will from time to time stand back to get a more general view of his work and to contemplate its wider relations. Indeed such intermissions are necessary, if he is to escape the tyranny of detail" _____

Collected Papers of Wilfred Trotter (1940) - London, p. 85.

CONTENTS

All per centage concentrations of the different constituents of the cerebrospinal fluid quoted in text and appendix refer to 100 cubic centimetres of the C.S.F. e.g. protein = 20 mgms. per cent - i.e. per 100 ccs. C.S.F.

INTRODUCTION

One hundred and eighty years ago, R. Whyte, then Professor of Medicine at Edinburgh University, first described tuberculous meningitis in a classic paper entitled 'Observations on Dropsy in the Brain'. This was one of the earliest types of meningitis to be recorded and was known as an acute hydrocephalus. Later, in 1825 Senn proved that this was of inflammatory origin and in 1830 Papaverine showed that meningeal and visceral tubercles were identical. Soon the different types of meningitis became differentiated following the introduction of lumbar puncture by Quincke (1891) and meningococcal meningitis due to Weichselbaum's diplococcus was distinguished by Comuline, Malling and Wright in 1898. The uniformly fatal character of the disease first described by Professor Whyte was widely recognised but, although there have been reported in the world literature many well authenticated cases in which a spontaneous recovery did occur[1,2,3,4], it was not until 1942 that Schatz, Bugie and Waksman, working at the New Jersey Experimental Station, New York, produced an antibacterial substance which offered some hope in altering this hitherto grave prognosis. This substance they called streptomycin after the organism streptomyces griseus from which it was obtained. This latter belonged to a group of aerial-mycelium producing and sporulating actinomycetes which had earlier been found to give rise, amongst other antibiotics, to a similar chemical compound streptothricin with, however, a wider and different antibacterial spectrum.

Streptomycin, it is interesting to note, was not the first antibiotic or substance found to have an anti-tuberculous, or tuberculostatic and tuberculocidal effect but it was the most recent and effective agent that could be used for practical application of treatment in Man. As early as 1885, that is three years after the isolation of the tubercle bacillus by Koch and one year after its description Cantani[6], on the basis of observations that the virulence of tuberculosis in corpses disappeared under the influence of putrefactive processes, used a common saprophytic organism, known as bacterium termo. A liquefied gelatin culture of this organism was given to a woman patient suffering from pulmonary tuberculosis with cavitation and, as a result of this early form of bacteriotherapy, the patient improved markedly, clinically, with reduction in the numbers of tubercle bacilli in the sputum.

In 1888 Babes[7] demonstrated that products of other saprophytic organisms had the capacity to inhibit the growth of tubercle bacilli and further he showed that streptococci, on the contrary, appeared to favour the development of the tuberculosis organism.

Somewhat later in 1893 Nannotti[8] observed that a tubercular inflammation of the knee joint tended to subside as a result of the spontaneous occurrence of erysipelas. Prudden[9] later concluded that there was no specific antagonism and that Nannotti's results were due simply to the related inflammatory responses caused by the accompanying organisms.

Between 1910 and 1913 Rappin[10] and Vaudremer[11], working on spore-forming bacteria and fungi respectively, established the sensitivity of the tubercle bacillus to the products of these various organisms.

Gradually it was thus established that the production of antituberculosis, or tuberculocidal and tuberculostatic agents was widespread amongst certain of the higher plants and amongst the various members of all the major groups of micro-organisms, namely, bacteria, fungi and actinomycetes. Further studies elicited that the activity of these agents was primarily due to certain well-defined chemical compounds which are now known as antibiotics. At least 11 bacterial preparations, 16 products of fungi, and 10 antibiotics of the actinomycetes have been isolated[12]. Amongst the bacteria, the bacillus subtilis group yielded subtilin as the tuberculostatic agent; and amongst the fungi, the aspergillus fumigatus group receiving particular attention, produced four antibiotics of which the common active principle was fumigacin. The actinomyces also produced four antibiotics, namely actinomycin, streptothricin, nocardin and the important streptomycin.

Of all these various agents, the streptomycin, appearing in 1944, seemed the most promising agent on account of its desirable physical and chemical properties, its low toxicity to animals and its pronounced effect on the tubercle bacillus in vitro and in vivo. This agent fulfilled what was then considered the desirable criteria[13] for a successful antituberculosis substance.

(a) The agent must be tolerated by the subject without producing irreversible physiological derangements;

(b) the progressive development of the disease must be reversed to non-progressive, accompanied by resolution, fibrosis, and calcification;

(c) the virulent infection must be eradicated and

(d) the effect must be produced in a reasonable time.

Following the discovery of streptomycin and its promise of value in the therapy of tuberculosis, in 1944 and 1945 Feldman, Hinshaw and Mann[14,15] pioneered the clinical investigation of the drug by treating guinea-pigs infected experimentally with the human type tubercle bacillus. They noted that streptomycin was well tolerated by the animals, that it exerted a striking suppressive action, that its action was probably bacteriostatic rather than bacteriocidal and concluded that the agent was worthy of trial in human beings. Garrod (1948)[16] disagreed in respect of the mode of action and produced experimental evidence to show that the drug was bacteriocidal especially in high concentrations. Nevertheless a year later Florey et alia (1949)[17] supported the original observation. Reports on the result of the use of streptomycin in various forms of human tuberculosis followed rapidly and Hinshaw, Feldman and Pfuetze (1946)[18,19,20] were able to report in a total series of 100 cases 12 with generalised haematogenous tuberculosis treated by streptomycin. Of these twelve cases nine presented clinical evidence of tuberculous meningitis and of these nine, four

were surviving at the time of the report. These four patients had had a well developed meningitis proved bacteriologically and all showed consistent and prompt improvement to therapy given by intramuscular and intrathecal routes. The condition of the cerebrospinal fluid improved, the mycobacterium (myco.) tuberculosis could no longer be obtained and recovery was such that treatment in three patients was discontinued after six months. However one of the three relapsed later, and all survivors suffered from marked neurological sequelae.

In spite of the only moderate success in this small series a clinical response to treatment, never before observed, had been obtained. Further series of treated cases confirmed that streptomycin had a suppressive and possibly curative action in meningeal tuberculosis and soon this antibiotic was being employed extensively as the main therapeutic weapon.

With increasing experience in its use and improvement in survival rates there have developed in the years subsequent to 1946 many different regimes involving continuous and interrupted therapy with streptomycin of different types, the use of varied routes of administration, the employment of adjuvant drugs, the display of neuro-surgical techniques, treatment with protein-purified derivative of tuberculin; and more recently newer agents that may supplant the streptomycin have become available. The most important of these newer preparations is isoniazid, one of two hydrazine derivatives of

isonicotinic acid. Thus with such variation in details of treatment it is not surprising that results reported from different centres have ranged from 11%[21] survival rate or lower up to 85%[22], care being taken in comparison to note the length of follow-up and whether the cases had been selected.

It would appear, therefore, that the time was opportune for a study of the different methods employed as a sufficient period had now elapsed for a satisfactory assessment, and so it is proposed to present in this paper a small series of cases of tuberculous meningitis treated with streptomycin by the combined intrathecal and intramuscular routes and in analysing and discussing the results to review the literature.

ANALYSIS OF RESULTS OF TREATMENT IN FIFTY-TWO CASES

During the period 1st October 1948 up to and including 31st December 1951 fifty-two consecutive cases, in which a clinical diagnosis of tuberculous meningitis was made, were admitted to a small unit reserved specially for the treatment of this disease. Complete laboratory facilities and a full range of specialist and consultant services were available. This series of cases included every admission whether moribund and dying within a few hours of admission or with minimal signs and symptoms.

Condition on Admission

The clinical state of cases often varied widely on admission and therefore the stage of disease was assessed according to the classification of the Streptomycin Sub-committee of the Scottish Scientific Advisory Committee[23]:-

Early:- Minimal physical signs; no neurological signs; mental confusion or irritability slight.

Intermediate:- Definite physical signs present; neurological signs present; mentally confused or disorientated and drowsy but able to answer questions or recognise parents.

Late:- In deep coma, or rousable by painful stimuli; unable to recognise parents.

In making the assessment most stress was laid upon the mental state as it was considered that this gave a very reliable criterion to the stage of the disease and reduced the amount of error that might arise through personal bias.

McCarthy and Mann (1950)[24] made this point in reporting a series of cases of tuberculous meningitis in children.

In the 52 admission to the unit 14 cases were in the early stage and 29% died, all of which were found clinically or later at post-mortem examination to have suffered also from extensive miliary disease. In the intermediate stage were 25 cases of which 64% died, this including four with miliary tuberculosis. In the late stage all 13 cases died and two had miliary disease and this gave, therefore, an overall mortality of 63.5%. All the cases that suffered from meningeal and diffuse haematogenous miliary lesions died. Table I below summarises these results.

Table I

Results of Treatment Related to Stage of Disease

Stage of Disease on Admission	Alive	Dead	Total
Early	10 (71%)	4* (29%)	14
Intermediate	9 (36%)	16 (64%) (12 + 4*)	25
Late	0	13 (100%) (11 + 2*)	13
Total	19 (36.5%)	33 (63.5%)	52

* Cases of tuberculous meningitis and miliary disease

Age on Admission

The age of the patient on admission was found to have a relationship to prognosis, a fact noted early by those centres employing streptomycin in treatment when the antibiotic was still under trial. Since the first large series of cases reported[25], it has almost universally been confirmed that the prognosis in those patients under three years old was much more serious than the older groups. This is demonstrated in Table II where four patients survived out of 20 aged three years or less whilst fifteen survived out of thirty-two cases above this age period - an almost 50% recovery rate. It was also noted that a higher proportion of the younger children were seen in an intermediate or late stage of the disease than in the older group and this is probably a reflection of the greater difficulty of earlier diagnosis in the very young child, thus giving a different prognosis for those different age groups.

Table II (A)

Results of Streptomycin Treatment in Relation to Age and Stage of Disease

Age on Admission in Years	Total	Alive				Dead			
		Total	Early	Intermediate	Late	Total	Early	Intermediate	Late
Under 1	4 (7.7%)	1	1	0	0	3	0	2	1
1 - 3	16 (30.8%)	3	2	1	0	13	1	5	7
4 - 6	7 (13.5%)	4	3	1	0	3	1	2	0
7 - 12	8 (15.6%)	5	2	3	0	3	1	1	1
13 and 13+	17 (13.4%)	6	2	4	0	11	1	6	4
Total	52	19	10	9	0	33	4	16	13

Table II (B)

Age	Total	Alive	Dead	Early	Intermed.	Late
3 years and under	20 (38.5%)	4	16	4	8	8
4 years and more	32 (61.5%)	15	17	10	17	15

Diagnosis

The diagnosis in each case was based on clinical history, family history especially with regard to contact with a tuberculous person or relative, the cerebrospinal fluid findings and bacteriology, the Mantoux reaction, examination of the fundus oculi, the radiological picture of the chest and the physical examination. These points are accordingly analysed in detail below.

Clinical History and Examination

With a view to ascertaining the most helpful clinical signs and symptoms that would lead to an early diagnosis the various manifestations with which the patient presented on admission were analysed. These are tabulated below in Table III and it can be seen that those presenting are of an insidious and non-specific character and often not necessarily pointing towards the nervous system. In fact there may be a striking absence of signs and symptoms, this being especially obvious in cases of miliary tuberculosis undergoing treatment and developing meningitis as a complication. For example cases may present atypically with alimentary symptoms and although none were found in this present series Smith and Vollum (1948)[26] and Rubie and Mohun (1949)[27] describe such instances.

A further Table IV below shows that there is no hard and fast relationship between length of history and stage of disease.

Conditions that appeared to have been precipitating factors were the respiratory illnesses in four cases, whooping cough in one, and measles in two. Trauma was a doubtful cause in two in one of which the child had received a minor injury to the head three weeks before admission, and in the other - case No. 26 - symptoms dated back to a fall from a bicycle two weeks prior to admission. However the stage of the disease was advanced on admission, the patient dying after nine days and so it is possible that the fall was the result rather than the precipitant of the illness.

It is of interest that two cases were examined thoroughly with full blood and radiological investigations for a transient pyrexial illness two months before admission. These examinations were carried out by a consultant physician and the findings were quite negative but three weeks later both cases had signs and symptoms suggestive of a tuberculous meningitis. This helps to stress just how insidious in onset the disease may be.

Another case illustrative of unusual presentation was admitted because of overdosage of morphine given by the practitioner to control a prolonged series of fits and the correct diagnosis was established the following day.

Study of Table III reveals that those symptoms of most frequent occurrence were those least specific in pointing to any special diagnosis. They were vomiting and headache; with lethargy, pyrexia, anorexia, constipation, coma, malaise and loss of weight less frequent.

Table III - Incidence of Symptoms and Signs on Admission

Clinical Manifestations	Total Number of Cases	Number of Cases in which Symptom Presented
Vomiting	38	6
Headache	35	16
Lethargy	15	7
Pyrexia	12	4
Anorexia	11	4
Constipation	10	1
Coma	9	0
Malaise	7	6
Loss of Weight	7	2
Respiratory Illness	4	3
Photophobia	4	0
Delirium	4	0
Irritability	3	0
Fits	3	1
Earache	2	0
Tonsillitis	2	1
Deafness	1	0
Perspiration	1	0
Weakness	1	0
Diplopia	2	1
Sensory Epilepsy with Dementia	1	0
Thirst	1	0
Neck Rigidity	40	0
Kernig and/or Brudzinski signs present	31	0
Papilloedema	10	0
Abnormal Eye Signs	3	0
Hypertensive Retinopathy	1	0
Abnormal Chest X-rays	33	0
Choroidal Tubercles	3	0
Paresis	7	0

The wide range of manifestations that can occur is also shown in the table, varying from thirst, earache, tonsillitis etc. to a sensory epilepsy. As regards signs, evidence of admission of meningeal irritation was usually present, neck rigidity being found in 40 cases and positive Kernig's and/or Brudzinski signs in 31, but this number is higher than that described by Rubie and Mohun (1949)[27]. Thus it is important to realise that there are cases of tuberculous meningitis, apart from those developing this as a complication to miliary disease and noted above, who present without the usual typical signs of meningeal irritation.

The symptomatology, therefore, is a vague one, easily overlooked in the small child and furthermore, confusing in that these symptoms may initially clear up for a short period before progressive deterioration sets in.

The table also shows that examination of the eyes is important as 14 cases had ocular signs and symptoms, all of which give valuable information towards a diagnosis. Headache is seen to be the earliest symptom, a finding with which the authors just mentioned agree but it can easily be overlooked unless the presence of a primary chest complex or active tuberculosis in the lungs or elsewhere in the body alerts one. Irritability, fatigue, failure to gain weight and personality change did not appear to be pronounced until the later intermediate stage of the disease developed.

Table IV

Length of History Related to Stage of Disease and Final Outcome

Length of History	Stage of Disease				Result	
	Early	Intermed.	Late	Total	Alive	Dead
1 week or less	12	3	1	16	9	7
2 weeks	2	8	3	13	4	9
3 weeks	0	5	3	8	2	6
4 to 7 weeks	0	4	2	6	1	5
8 weeks or more	1	4	4	9	3	6

Table IV reveals one or two interesting points in that the general pattern shows that a short history is related to the disease in the early stage and thus gives a better prognosis, and that as the duration of symptoms and signs lengthens so, as one might expect, more cases are admitted at a later stage and the prognosis becomes graver with a higher mortality. This is true up to two months or more and then the pattern remains more or less fixed without a relative increase in mortality. Nevertheless there are sufficient cases surviving with a long duration of symptoms and sufficient cases dying even after a history of only one weeks ill-health to show that one cannot employ the duration of history before admission as a criterion on which to base the estimation of the stage of the disease or to assess, what is more difficult and important, the prognosis. As an example of this, one case with a history of under one week was admitted in an advanced state and conversely one

case was early after an eight weeks history as shown by the table.

These observations could be criticised on the grounds of the small numbers of cases involved in each grouping but they do confirm the impressions gained by most other clinicians.

Family History

Following admission and the obtaining of a history of the illness enquiry was next made into the family history to determine if any contact with a tuberculous person had occurred. A definite history of contact was obtained in 14 out of 50 cases. Of these 14 the source of the infection was the father in four, the mother in five, a sibling in two and a more distant relative in three. In two cases no family history was obtained and the remainder gave a negative story of contact. This figure of positive contact is much less than that quoted by the Medical Research Council (1948)[25] but is in keeping with many other centres. One's own opinion is that the figure is too low and a fuller and more vigorous enquiry into the health of the immediate family circle would increase the total and give a more accurate result.

Case No. 25 gave no history of contact with a tuberculous person but the child had been fed on unpasteurised milk and later a positive culture from the cerebrospinal fluid was obtained yielding a bovine strain of the tubercle bacillus.

Tuberculin Reaction (Mantoux)

This was carried out in 47 cases as a useful aid towards diagnosis. The usual technique employed was to use on the forearm intracutaneously with a control on the other first a dilution of 1 in 10,000 and to increase the strength to 1 in 1,000 or further to 1 in 100 if negative responses were obtained. A skin area of oedema and redness of one centimetre appearing within forty-eight hours was considered a positive reaction and this occurred in 44 out of these 47 cases. In the remaining three, a negative reaction was obtained in one, death taking place before a stronger test solution could be used, and the two other cases were advanced and may have been examples of anergy. (Lincoln and Sifontes(1953)[28] believe anergy to be rare).

Five cases remain in which the test could not be completed because of early death soon after admission.

Cathie and Macfarlane (1950)[29] report the use of 1 in 100 dilution only, routinely, and so the custom in the later cases was to carry out the mantoux test first with the dilution of 1 in 1,000 tuberculin and discard the higher dilution. This often saved time and led to no untoward reactions.

Examination of the Eye

Special attention was paid to retinoscopy and examination of the eye when the patient was admitted. In the cases of very young children, especially those irritable and restless on admission, this entailed considerable patience

and some difficulty, 1% homatropine sulphate being used to dilate the pupil. At the time this was deemed to be satisfactory without the additional use of sedation as suggested by Illingworth and Wright (1948)[30] and Emery and Lorber (1950)[31].

In this series choroidal tubercles were seen in only three patients all of whom suffered from a miliary and meningeal infection. This number gives a much lower incidence than in the majority of series reported and would suggest that examination under sedation or anaesthesia should be tried in the future.

In these three cases all of whom died eventually in spite of 102, 110 and 48 days of treatment respectively changes in the tubercles were observed in that they became paler and better defined whilst in one pigmentation appeared around the edge of the lesion. These changes suggested that healing was occurring and might indicate an improving prognosis in these cases but nevertheless all succumbed. However none of these tubercles became parchment white which Illingworth and Wright in their careful survey stressed, was the only stage at which one could venture to say that the prognosis was definitely better, although healing changes were a good rather than bad sign.

10 cases showed the presence of bilateral papilloedema and in case No. 15 the papilloedema was followed by the development of bilateral optic atrophy. In this patient, the condition deteriorated in spite of therapy with the

appearance of ocular palsies, mental hallucination and attacks of vomiting with headache. The cerebrospinal fluid had a high cell count with moderate increase in the protein level and was under increased pressure and so a block to the fluid circulation in the region of the basal cisterns was suspected. Further neuro-surgical intervention to relieve the increased intracranial pressure should have been carried out in this patient earlier, this case being an example whereby the eye signs gave early warning of the developing complication.

One other case had an abnormal retinal pattern in that increased tortuosity and narrowing of the retinal arteries was present this being accompanied by a blood pressure of 210/130. This case resembled in this respect that described by Cairns and Taylor (1949)[32] in which the presence of arterial hypertension was correlated to the increase in intracranial tension, the hydrocephalus, and the basal adhesions constricting and affecting hypothalamic function.

Radiological Findings

Routine chest radiography was positive in 33 cases and out of the remaining 19, six patients were too ill to X-ray, three dying shortly after admission and the three others surviving for a few days in a moribund condition.

The radiological findings consisted of evidence of pulmonary miliary tuberculosis in ten, enlargement of the hilar glands with or without evidence of the complete primary

complex in a further ten, and other types of tuberculous lung lesions in a further nine cases, e.g. apical infiltration with or without cavitation, a tuberculous bronchopneumonia, and tuberculous consolidation. The remaining four patients had pleural effusions without obvious underlying parenchymal disease.

Cases worthy of more detailed mention are Nos. 6, 11, 16, 43 and 47. In case No. 6, a girl aged 18 years old, no radiological evidence of pulmonary tuberculosis was apparent during the treatment of her tuberculous meningitis but later, when the latter infection seemed undoubtedly cured, she developed enlargement of the tracheo-bronchial lymph glands resembling rather the hilar adenitis accompanying the primary complex in childhood and later, as this latter improved, a left upper lobe consolidation of tuberculous aetiology developed. The lung lesion and her general condition initially responded to further intramuscular streptomycin and para-aminosalicylic acid (P.A.S.) therapy under sanatorium conditions and there was no sign of a relapse of her tuberculous meningitis, but subsequent deterioration in the pulmonary condition occurred and a left upper lobectomy had to be performed. The patient is now well and a photograph of the lobe removed can be seen in the Appendix.

Case No. 11 had apical tuberculosis with cavitation on the left side and died from his pulmonary disease after a second stage thoracoplasty operation. His death occurred one year after clinical cure of his meningitis and

at post-mortem examination the brain appeared normal in appearance with only slight thickening of the pia-arachnoid mater around the base. No tubercles were to be seen along the vessels in the Sylvian fissures and there was no dilatation of the ventricles. For this reason this case has been included in the successes of treatment for meningitis. However the lungs showed extensive tuberculous infiltration with chronic cavitation and an empyema in the left pleural cavity. A few small areas of tubercular invasion were present in the right lung. Here then is a case where earlier surgical intervention, for example during the second half of the treatment of his meningitis, might have altered the eventual outcome.

Case No. 16 in addition to the lung lesion had a tuberculous polyserositis affecting pericardium, peritoneum, pleura and of course the meninges, and she also developed a paravertebral abscess. The autopsy suggested that death was due more to the widespread advanced tuberculous lesions than to the meningitis which histologically was in the early stage.

Case No. 43 also had multiple lesions in that a pleural effusion, a peritonitis and a paravertebral abscess was present.

Case No. 47 was of interest in that a presumed serous tuberculous meningitis developed whilst the child was undergoing treatment for a lesion causing a dense homogenous shadow in the right upper lobe and spreading to

the right middle lobe. At various times the pathology was considered to be an empyema, a consolidation and an epituberculous allergic reaction but it was not until a lung puncture was performed and caseous material swarming with tubercle bacilli obtained that the suspected tuberculous aetiology was confirmed. Gradual clearing of this shadow, due therefore to a tuberculous lobar pneumonia, has occurred and examples of some of the X-ray films taken are shown in the Appendix. The child's condition is now excellent.

Tuberculosis elsewhere in those patients with chest lesions was noted in three other cases in addition to those described above, one having a peritonitis, one a salpingitis (presumptive diagnosis) and one a perisplenitis. One other case with the chest radiologically clear suffered from a tuberculous osteomyelitis affecting the head and shaft of the left femur with also involvement of the hip joint on that side.

Table V stresses what we have already noted that miliary disease whether pulmonary, or disseminated generally throughout the body, gives a grave prognosis and in the Medical Research Countil series (1948)[25] where recent primary lung lesions are grouped with miliary this higher mortality is evidenced. The other types of lung disease do not appear to have such an adverse bearing on the outcome of the meningitis but naturally a clear radiological picture will give the better prognosis.

Table V - Results Related to Radiological Findings

Radiological Findings	Number of Cases	Alive	Dead
1. Enlargement of Hilar Glands or Primary Complex	10	6 (60%)	4 (40%)
2. Miliary Lung Disease	10	0	10 (100%)
3. Pleural Effusion	4	2 (50%)	2 (50%)
4. Other Tuberculous Chest Manifestations	9	5 (55%)	4 (45%)
5. Radiologically Clear	13	6 (46%)	7 (54%)

Bacteriology

Bacteriological proof of the diagnosis was obtained in 37 cases by a positive guinea-pig inoculation and in a further eight of the remaining 15 cases this proof was gained by culture and/or post-mortem examination (five cases by culture and three by autopsy). This leaves seven cases in which the diagnosis was based on findings other than bacteriological and these will be presented below. The routine employed in each case was to examine the cerebro-spinal fluid by film, culture and by animal inoculation to obtain the causative organism. The guinea-pig test was carried out in 51 of the 52 cases with the above mentioned positive results, and culture of the fluid was positive in 34 of the 50 cases in which it was performed. Culture yielded a human strain in 30 and a bovine in 4 cases, and it was positive in 5 patients where the animal inoculation failed.

In almost all of the 7 cases in which no bacteriological proof was obtained strong presumptive evidence including response to therapy and pattern of cerebrospinal fluid change, was present. These seven cases were Nos. 12, 29, 39, 40, 44, 45 and 47.

Case No. 12 was a moribund child aged 1½ years who was too ill to X-ray and who died before the mantoux test could be read. Cerebrospinal fluid however showed the changes suggestive of an advanced tuberculous meningitis, with marked reduction in sugar and chloride levels and elevated protein and cell count levels, the latter being predominantly lymphocytic.

Case No. 29 was a wasted dehydrated child, aged 1¾ years, admitted with a vague three week history of symptoms, a left ptosis, and facial palsy and a spastic left hemiparesis. The cell count in the cerebrospinal fluid was normal until streptomycin was given intrathecally, when a slight rise took place. The protein level was raised, the sugar reduced and the chloride normal. Mantoux test was very strongly positive. Decerebrate rigidity developed and the child died on the thirteenth day. During life no fundal changes were observed and the child was too ill to X-ray. The diagnosis was based on the above clinical picture and the disease was presumed to be advanced with extensive basal adhesions.

There are more grounds for argument as to the correctness of the diagnosis in case No. 39. The marked

fluctuations in the cerebrospinal fluid cell count (mainly lymphocytic) and protein levels seemed to be related to the intrathecal administration of streptokinase and were not a true reflection of the common pattern found in tuberculous meningitis. Sugar level was within normal limits but chloride level was reduced. Bacteriology was negative but the mantoux test was strongly positive. Differentiation from other lymphocytic meningitides and influenzal meningitis was very difficult.

Case 40 resembled the latter but there were the typical spiking in the cell counts and protein levels on a graph of the changes in the cerebrospinal fluid elements which suggest tuberculous meningitis. The mantoux test was strongly positive and the cells and protein were raised, and the sugar and chloride lowered in the cerebrospinal fluid on admission. Graphs of the behaviour of the constituents of the latter are included in the Appendix along with these two case notes.

Case No. 44 was unusual in that she had been admitted eight years previously for neuro-surgical investigation of momentary sensory epileptiform attacks and the examination then was completely negative, an inflammatory focus such as a tuberculoma or a cortical scar being postulated as the cause. Symptoms resolved spontaneously during the intervening period to recur once again heralding in a new illness in which she became irritable, drowsy and demented, and wasted. Her sensory phenomena disappeared after admission

but she was now suffering from a tuberculous meningitis with typical changes in the cerebrospinal fluid suggesting advanced disease. Permission for autopsy was refused.

In case No. 45 a very bad family history of tuberculosis, a chest X-ray showing right middle lobe consolidation and a positive mantoux test all helped towards the diagnosis of a simple serous tuberculous meningitis as described by Lincoln (1947)[33]. The child was aged eight months and was undergoing treatment for his chest lesion when a deterioration in condition led to a diagnostic lumbar puncture and this obtained a lymphocytic cerebrospinal fluid with a normal chemistry and negative bacteriology. It was considered safer and wiser to treat with a shortened course of intramuscular and intrathecal streptomycin and the graph of the behaviour of the cerebrospinal fluid shows how it returned to normal in eleven weeks after showing a fluctuating pattern. This behaviour would tend to confirm the diagnosis and exclude a meningo-encephalitis following chickenpox the rash of which the child developed a few days earlier. This latter was very seriously considered for a time as an alternative diagnosis.

The clinical details of the last case No. 47 with a negative cerebrospinal bacteriology have already been described under the paragraphs on radiological findings (page 21). This child during treatment of his caseous right upper lobe pneumonia became irritable, had a headache and developed a pyrexia which was charted even higher by error. A diagnostic lumbar puncture was accordingly carried out and

revealed a cerebrospinal fluid similar to that in case No. 45. In view of the whole clinical background streptomycin was given for a short period by combined routes but the cerebrospinal fluid rapidly returned to within normal limits. There was also in this case a family history of tuberculosis and the mantoux test was strongly positive. Seven weeks therapy for the presumed serous meningitis was given in this instance.

Bacterial resistance to streptomycin developed in three cases. In No. 30 meningitis developed during treatment of generalised miliary disease and the child eventually died, the resistant organism being obtained at post-mortem examination. In No. 33 resistance developed during treatment for a relapse and a satisfactory response occurred only when iso-nicotynal hydrazine (isoniazid) was used. The third case was No. 11 the resistant organism being obtained from the sputum after clinical cure of his meningitis as described on page 20 under the heading of radiological findings.

Differential Diagnosis and the Cerebrospinal Fluid

Differential diagnosis could be difficult in an atypical case especially in view of the insidious onset and vague symptomatology and therefore examination of the cerebrospinal fluid formed the most important part in the routine of examination, positive bacteriology obtained by film, by cultural methods or animal inoculation as already mentioned, clinching the diagnosis.

The normal levels for cerebrospinal fluid constituents was considered to be:- cells: 0 - 5 per cubic millimetre (per cu.mm.); protein: 20 - 40 milligrams per cent (mgms.%); sugar: 45 - 55 milligrams per cent (mgms.%) and chlorides: 690 - 750 milligrams per cent (mgms.%). Various conditions that might have to be considered in differential diagnosis were poliomyelitis, benign lymphocytic chorio-meningitis, and other virus meningitides and encephalitides, disseminated sclerosis, intracranial abscess or neoplasm, haemophilus influenzae meningitis, pyogenic meningitis, tuberculoma, Weil's disease, glandular fever, cerebrovascular accident, mumps or whooping cough encephalitis, lateral sinus thrombosis, torulosis, coccidioides etc. etc. That this range of conditions for consideration is not too excessive is borne out by the varied presumptive and actual diagnosis in cases admitted as tuberculous meningitis to the special centre at Oxford under Smith, Vollum and Cairns (1948)[34].

As many cases of poliomyelitis were admitted to the other wards during the period over which this series of cases was analysed the opportunity is taken to compare the initial findings in the cerebrospinal fluid (C.S.F.) on admission in the cases of tuberculous meningitis, poliomyelitis and also in some cases of the other types of meningeal infection, and these results are tabulated below. Admissions to neighbouring hospitals are also included in this table.

Table VI

1. Comparison of Initial C.S.F. Cell Counts

Cells per cu.mm.	Tuberculous Meningitis	Poliomyelitis	Lymphocytic (Chorio)meningitis	Influenzal Meningitis	Meningococcal Meningitis	Pneumococcal Meningitis	Staphylococcal Meningitis	Other Pyogenic Meningitis
0 - 5	-	15	1	-	1	-	-	-
6 - 10	1	6	-	-	-	-	-	-
11 - 20	3	19	3	-	-	-	-	-
21 - 40	2	15	3	-	-	-	-	-
41 - 60	5	9	4	-	-	-	-	-
61 - 80	3	6	-	-	-	-	-	-
81 - 100	7	7	-	-	-	-	-	1
101 - 150	10	10	-	-	1	-	-	-
151 - 200	17	2	2	-	-	-	-	-
201 - 300	16	7	3	-	-	-	-	-
301 - 400	7	1	1	-	-	-	-	-
401 - 500	5	3	2	-	1	1	-	-
501 and over	3	-	-	3	7	-	5	2
Total	79	100	19	3	10	1	5	3

2. Comparison of Initial C.S.F. Protein Levels

Protein in mgms.%	Tuberculous Meningitis	Poliomyelitis	Lymphocytic (Chorio) meningitis	Influenzal Meningitis	Meningococcal Meningitis	Pneumococcal Meningitis	Staphylococcal Meningitis	Other Pyogenic Meningitis
0 - 10	1	5	4	-	1	-	-	1
11 - 20	4	26	4	1	1	-	-	-
21 - 30	1	25	6	-	-	-	-	1
31 - 40	11	8	2	-	-	-	-	-
41 - 50	3	10	2	-	-	1	-	-
51 - 60	9	4	1	-	-	-	-	1
61 - 70	4	6	-	-	1	-	-	-
71 - 80	10	-	-	-	-	-	-	-
81 - 90	3	6	-	-	2	-	-	-
91 - 100	6	2	-	1	-	-	-	-
101 - 150	13	4	-	-	2	-	1	-
151 - 200	4	1	-	-	-	-	-	-
201 and over	11	1	-	-	1	-	4	-
Total	80	98	19	2	8	1	5	3

3. Comparison of Initial C.S.F. Sugar Levels

Sugar in mgms.%	Tuberculous Meningitis	Poliomyelitis	Lymphocytic (Chorio)meningitis	Influenzal Meningitis	Meningococcal Meningitis	Pneumococcal Meningitis	Staphylococcal Meningitis	Other Pyogenic Meningitis
60 and over	2	24	6	-	-	1	-	1
59 - 50	2	21	6	-	-	-	1	1
49 - 40	9	2	3	-	-	-	-	-
39 - 30	11	5	1	1	-	-	-	-
29 - 20	15	-	1	-	-	-	2	-
19 - 10	14	-	-	-	2	-	-	-
9 - 0	9	-	-	1	3	-	-	1
Total	62	52	17	2	5	1	3	3

4. Comparison of Initial C.S.F. Chloride Levels

Chlorides in mgms.%	Tuberculous Meningitis	Poliomyelitis	Lymphocytic (Chorio)meningitis	Influenzal Meningitis	Meningococcal Meningitis	Pneumococcal Meningitis	Staphylococcal Meningitis	Other Pyogenic Meningitis
750 - 690	14	42	15	-	-	-	-	1
689 - 680	3	-	-	-	1	1	-	-
679 - 670	6	2	-	-	2	-	1	-
669 - 660	8	1	-	-	1	-	-	-
659 - 650	1	-	-	-	-	-	1	-
649 - 640	5	-	-	-	-	-	-	-
639 - 630	5	-	-	-	-	-	-	-
629 - 620	8	-	-	-	-	-	-	-
619 - 610	1	-	-	-	-	-	-	-
609 - 600	4	-	-	1	-	-	-	-
Under 600	4	-	-	-	-	-	1	-
Total	59	45	15	1	4	1	3	1

The only figures in the above table which are really worthy of comparison are those of tuberculous meningitis, poliomyelitis and other forms of lymphocytic meningitis as the number of cases in the remaining diseases are too small. In respect of the cell counts one notes that in the pyogenic meningitides and influenzal meningitis the cell counts are very high and predominantly polymorphonuclear. However, when the count is mainly lymphocytic, the number of cells per cubic millimetre does not appear in itself to be of value in differentiation of disease.

In the case of the protein levels a high proportion in the virus meningeal infections are within normal limits as compared with tuberculous meningitis. However there are a sufficient number within each disease group both within normal and above normal to show that the protein level on its own is not an absolute criterion towards diagnosis. In the remaining diseases the protein levels tended to be high.

On looking at chart (3) however, sugar levels can be seen to be much more helpful and a low level accompanying a predominantly lymphocytic cell count will definitely favour a tuberculous meningitis and as a corollary if the cell count has many more polymorphs a pyogenic meningitis is more probable.

Chloride levels also helped as it was in tuberculous meningitis that they were characteristically lowered. Nevertheless one should note that 14 cases of the latter

disease had normal chloride values.

Table VI thus demonstrates the different features of the cerebrospinal fluid in the diseases mentioned and the overall picture agrees with that presented in the standard textbooks. The point to note is the number of cases which are borderline and cause variation in the typical cerebrospinal fluid pattern commonly described. Initial cerebrospinal fluid results may not be easy to evaluate and therefore assessment should be made, in these instances, on the results of further lumbar punctures taken in conjunction with the clinical and radiological picture.

Cerebrospinal Fluid Changes during Therapy

In each case the cerebrospinal fluid was withdrawn at lumbar or intrathecal puncture and sent for examination. Owing to the many demands on laboratory staff protein levels and the cell counts only were estimated on each sample. Full chemistry and bacteriology was performed on the first few specimens at the commencement of therapy and then also at two to three weekly intervals. It was considered that the protein and cell count levels were of most importance especially in order to detect early any signs of the development of a spinal block. Later, as cell count and protein level often took a prolonged time to return to the normal levels which have been quoted above, it was found chloride and especially the sugar levels in their return to normal values were helpful in judging clinical cure, and when to discontinue therapy.

A constant feature in the majority of cases was a rise, often very marked, in the number of cells on commencement of intrathecal therapy and this with other points will be raised again in the discussion which follows later. In those patients who made a satisfactory progress with good prognosis the protein level and cell counts gradually and steadily returned to normal with accompanying rise in the sugar and chloride values. Usually normality was approached about 40 - 60th day of therapy but actual attainment of the physiological level took much longer with the sugar and chloride, then the cell count and finally the protein in that order reaching their normal figures. This pattern described is shown in cases Nos. 5, 11, 20, 22, 23, 33, 34, 35, 38, 39, 40, 41, 50 and 51.

A second pattern of change was manifest in cases who deteriorated and the main feature was a falling sugar and chloride level or one that remained below normal without rise. This was apparent in cases Nos. 3, 7, 8, 9, 14, 15, 19, 25, 26, 27, 28, 32, 43, 48 and 52.

Patients who died on admission or shortly afterwards usually presented a cerebrospinal fluid picture in which the cell count and protein figures were very high and the sugar and chloride levels very low. This pattern accompanied advanced disease and gave a bad prognosis. Cases Nos. 4, 36 and 49 exemplify.

Improvement in the cell count and protein level was noted to occasionally occur during rest periods when no intrathecal therapy was given.

A very high protein value with low cell count was present in cases Nos. 1, 6, 18 and 31 and this along with other signs e.g. xanthochromia,+ve Queckenstedt test was taken to indicate a block, possibly in the spinal subarachnoid space, and in two of these four patients autopsy confirmed this. In case No. 17 high cell counts accompanied very high protein levels and this suggested exudate and adhesions causing a basal cistern or subtentorial block along with an active infection. These raised cell counts were considered to indicate an active infection and their return to normal a clearing of the meningitic process. Some cases were noted in which death occurred soon after admission with very few changes in the cerebrospinal fluid. Post-mortem examination in confirming the diagnosis usually explained this picture in that marked hydrocephalus and extensive basal adhesions were present, the latter locking up the foci of infection. Yet again therapy could control the infection and the late result of the meningitis, that is these adhesions and a tuberculous arteritis,would kill the patient. Cases 9, 13 and 21 exemplify.

In three cases (Nos. 16, 32 and 46) with miliary disease, death occurred in spite of cerebrospinal fluid examinations suggesting a mild meningitis.

Streptomycin assays on lumbar and cisternal fluid were performed in suspected cases of spinal subarachnoid block and,in one instance, showed no diffusion of the streptomycin upwards to the cisterna magna from the lumbar region. As

these assays were carried out in too few cases further analysis of the results have not been attempted.

Clinical Course under Treatment

The progress of each case had its own individual variations but nevertheless certain common patterns were discernible and for descriptive purposes could be divided into a group in which the patients survived and one in which they died.

In the latter group were those cases which did not respond to treatment in which a temperature with average peaks of over 100°F. persisted and only became subnormal in some cases a few days before death. Examples of this pattern were cases Nos. 3, 4, 7, 8, 19, 24, 25, 26, 29, 32, 44 and 52. These patients never showed at any time signs of improvement and deteriorated steadily. A second pattern in cases who died was that of an initial satisfactory clinical response with later deterioration usually from the late effects of the disease as has been described. Cases Nos. 14, 15 and 21 fall into this category. Cases Nos. 13, 27, 31, 37 and 46 also were patients who progressed well initially and prognosis appeared good only to deteriorate at a late stage from a recrudescence in some instances when intrathecal therapy was less intense. Finally there was the group of cases in which death occurred within a few hours or days of admission. They remained moribund and temperature was high or subnormal, death occurring before any clinical effect of treatment could be obtained. Cases Nos. 2, 10, 16, 28, 36, 42, 48 and 49 are examples.

Meningitis developed after presumed cure of a pulmonary miliary infection in cases Nos. 14 and 46 and developed during treatment of a similar lung infection in cases Nos. 24 and 30. The clinical pattern in cases Nos. 14 and 30 was one of progressive deterioration, death in the former being associated with a spinal subarachnoid block and in the latter with a resistant organism, already noted above.

Both case 24 and 46 improved initially and one was hopeful of eventual cure but later deterioration and death took place being especially disappointing in case No. 46 who at one time seemed to be making excellent progress. The late effects of the disease rather than an active infection was the cause of death here.

Temperature chart, and pulse and respiratory rates in these fatal cases described above often bore no relationship to the seriousness of the patient's condition in tuberculous meningitis and could be normal for two to three weeks before death.

In the other group of cases making satisfactory progress there were firstly those which showed an uninterrupted improvement (cases Nos. 5, 11, 20, 22, 23, 34, 35, 38, 39, 40, 41, 45, 47, 50 and 51). In the majority of these patients the temperature averaged 100°F. for the first 10 - 14 days then fell with average peaking up to 99°F. for a further three to five weeks, this fall coinciding with a general clinical response to therapy and this response was then followed by steady improvement in physical and mental well-being with weight gain.

Case No. 1 also showed a steady improvement but only after an initial stationary period.

Cases 17 and 33 relapsed after improvement and following a further complete course of streptomycin therapy by combined routes became and remained well.

The remaining case that survived is number six an outline of the radiological findings in the chest being described under that heading on page 20. This patient developed subarachnoid block in the thoracic region of the spinal cord early in therapy and as a result of further neuro-surgical investigation streptomycin was given into the ventricles through frontal burr holes. Convulsions followed; the patient became comatose and developed a complete paraplegia with urinary and faecal incontinence. Subsequently streptomycin therapy was administered only by the intramuscular route and the patient surprisingly improved so that rehabilitation could eventually be commenced. The patient was left with a complete bilateral nerve deafness and spastic lower limbs but with the help of special training and exercises managed to gain control of bowel and bladder function and walk with the help of calipers. The hearing defect was successfully overcome by teaching her lip-reading. The subsequent progress with development of enlarged tracheobronchial lymph glands, left upper lobe pneumonia and lobectomy have already been outlined.

These clinical patterns of response to therapy which have just been described are in accord with those found by other workers (Med.Res.Co. (1948)[25])

Complications occurring during Therapy or Found at Autopsy (in association with the disease process)

Amongst the 52 cases of this series only nine could be said to have no complications or lesions present in addition to their tuberculous meningitis and of these nine cases two were too ill to investigate completely both dying shortly after admission (cases Nos. 26 and 42). In the majority of cases the accompanying pathology was in the chest and in ten instances consisted of a miliary tuberculosis of the lungs as has already been mentioned. Twenty-three cases were complicated by lung lesions other than the miliary dissemination and in nine patients a block in the cerebrospinal fluid circulation was suspected or confirmed. Of these nine, the block appeared to be in the region of the basal cisterns in seven, in the thoracic region of the spinal cord in one (case No. 6) and in the last case there was a block present in the upper thoracic region of the spinal cord and in the basal cisterns close to the opening of the tentorium cerebelli (case No. 18).

Hydrocephalus was noted clinically or at post-mortem examination in eleven patients, in three of whom it was mild in degree (cases Nos. 3, 21 and 24).

Other complications noted are summarised in Table VII below.

Table VII - Complications found during Therapy or at Post-Mortem Examination (excluding those arising from therapeutic method)

Pulmonary Lesions	23
Pulmonary Miliary Lesions	10
Block in the Cerebrospinal Fluid Circulation	9
Hydrocephalus	11
Tuberculous Disease of the Spine	2
Decerebrate Rigidity	3
Spastic Quadriplegia	3
Hemiplegia	4
Tuberculous Peritonitis	3
Tuberculous Myocarditis (1 case with tuberculous abscess in left ventricular muscle)	3
Tuberculous Ileitis	1
Tuberculous Salpingitis	1
Tuberculous Renal Lesions	1
Tuberculous Perisplenitis	1
Tuberculous Osteomyelitis (left femur and hip joint)	1
Optic Atrophy	2
Hemianopia	1
Speech Defect	2
Behaviour Problem	1
Abortion	1
Tuberculous Cervical Abscess	1
Median Nerve Palsy	1
Septicaemic Miliary Disease (with lesions in lungs, liver, spleen, peritoneum, kidneys etc.)	4

Post-Mortem Results

Of the 33 cases who died permission for post-mortem examination was obtained in 17. A constant picture was noted consisting of a gelatinous basal exudate around the brain stem with fibrous adhesions which in one case were actually seen to compress slightly the medulla oblongata. Hydrocephalus in varying degree was a constant concomitant and usually the fibrous adhesions seemed to interfere with the cerebrospinal fluid circulation in the region of the basal cisterns and around the cerebral peduncles. The foramina of Luschka and Magendie were clearly seen to be blocked in four cases. Tubercles were usually seen in the perivascular spaces alongside the blood vessels and spread commonly into the Sylvian fissures. Involvement of the ependyma was noted in seven cases and of the choroid plexus in three cases. Case No. 42 had a tuberculoma of the pons and in Case No. 7 tuberculous granulation tissue surrounded and compressed the optic nerves.

The post-mortem appearances with satisfactory clearing have already been described in case No. 11 on page 21.

Case No. 21, who suffered also from miliary pulmonary disease showed radiological clearing of the latter before death but at autopsy tubercles were still obviously scattered throughout the lung fields.

Case No. 46 who was admitted with a relapse of her pulmonary miliary disease and a tuberculous meningitis showed radiological and post-mortem clearing of the lung lesions

although death resulted from the meningitis which was seen to be still active. Extensive adhesions present at post-mortem confirmed the clinical impression before death that these were a contributory factor in the failure of therapy.

Finally case No. 18, in which protein purified derivative of tuberculin (P.P.D.) was given intrathecally, died as a result of hydrocephalus and blocks to the cerebro-spinal fluid circulation. At autopsy macroscopically the disease seemed arrested with many fibrous adhesions present but histologically active foci of infection could still be detected.

Treatment

A. Streptomycin Therapy

Streptomycin as the calcium chloride complex or as the sulphate, or dihydrostreptomycin was employed in each case in this present series with the exception of two both of which were moribund on admission. Intrathecal and intramuscular routes were used in all cases including those instances of recrudescence or relapse. The dosage factor varied according to age, expected weight taking into consideration also body build and height, and the severity of the disease. Initially adults were given 2 Gm. daily by the intramuscular route but this was later reduced with no apparent loss of efficiency to 1 Gm. daily. In children the dosage was usually about 0.5 Gm. daily and in infants a correspondingly smaller total daily dose was given. For

calculation of the latter the factor 0.02 Gm. per pound body weight per day was employed but in some cases a slightly less dose than this would have allowed, was given. The intramuscular dose was divided into injections given twice daily, i.e. in the morning and the evening.

Intrathecal dosage was 0.1 Gm. for adults and a proportional dosage between 0.05 Gm. to 0.1 Gm. for children of five years or more, the streptomycin being given slowly dilated in 5 - 10 ccs. of normal saline well admixed with cerebrospinal fluid. For younger children and infants less than 0.05 Gm. was given the smallest dose being 0.02 Gm. in a seven months old baby. Intrathecal administration was usually performed six hours after the morning intramuscular injection; that is to say midway between the two latter daily doses.

The rhythm and principles of the treatment regime was here again the same for all cases but varied in detail from patient to patient according to the stage of the disease on admission, their clinical progress and the development or otherwise of complications such as blocks to the cerebrospinal fluid circulation. The rhythm of therapy consisted of an initial period of seven to fourteen days intense treatment in which daily intrathecal injections were given. The next period in certain cases, consisted of the injections being given on alternate days up to the fourth or sixth weeks. Then if progress was favourable the injections were given thrice weekly thus allowing a short

rest at the week-end welcomed by patient and doctor alike. This thrice weekly routine was employed, however, in the majority of patients after the initial period of daily punctures. At the end of 12 - 16 weeks of treatment a careful review of progress was made to determine if a rest period off treatment could be safely allowed. In only a very few exceptional cases was this rest interval permitted earlier. Throughout this first basic 12 week course intramuscular treatment was given as detailed above.

After this rest period usually of one to two weeks duration, if the clinical state and cerebrospinal fluid findings still suggested that the infection was active, a further course of treatment was given in the form of weekly intrathecal injections with the twice daily intramuscular dosage as before. After four weeks reassessment was done and if necessary this latter routine repeated after the second rest period.

Should the clinical assessment at any rest period suggest the infection was still active, a reversion to the thrice weekly intrathecal punctures along with the usual intramuscular schedule was made and after the four weeks once again the rest period and the assessment. With improvement the less intense routine would then be given as detailed above.

When this periodic evaluation at a rest period suggested that the infection was fully controlled with cerebrospinal fluid findings approaching normal especially

in respect of the sugar levels then intrathecal treatment was discontinued but intramuscular therapy was given for a further two months. This latter treatment was carried out during in-patient and out-patient surveillance but a most careful follow-up was insisted upon in respect of the latter. During out-patient attendance the case was admitted for 48 hours for complete check every two or three weeks up to the third month from hospital discharge. Attendances then became less frequent at monthly intervals: other points in connection with this follow-up detail will be mentioned later.

In sixteen cases the calcium chloride complex of streptomycin was used with a survival rate of five. However there was a high proportion of late and intermediate cases within this group. Later dihydrostreptomycin was employed with the hope of greater efficacy and lessened incidence of vestibular upset and 29 cases were treated, 12 surviving. A high incidence of deafness followed its use and so the last four cases in the series were treated with streptomycin sulphate of which two recovered. Case 46 was treated with dihydrostreptomycin and a recrudescence of the disease was then treated with streptomycin sulphate.

If those cases which had repeat courses of treatment because of a relapse or a recrudescence are included, the relapse in two further patients was treated with dihydro-streptomycin, one dying and one surviving. The relapse in two other patients was treated with streptomycin sulphate and both cases survived.

Table VIII in summarising these results shows that the numbers in each group are too small for statistical comparison.

Table VIII - Results of Treatment Correlated to Type of Streptomycin Employed

Type of Antibiotic	Alive				Dead				Total
	Early	Intermediate	Late	Total	Early	Intermediate	Late	Total	
Calcium Chloride Complex of Streptomycin	0	5*	0	5*	1	5	5	11	16*
Dihydrostreptomycin	9+	3	0	12+	3	10	4	17	29+
Streptomycin Sulphate	1	1	0	2	0	0	2	2	4
Dihydrostreptomycin and Streptomycin Sulphate	0	0	0	0	0	1	0	1	1
No Therapy	0	0	0	0	0	0	2	2	2
Total	10	9	0	19	4	16	13	33	52

* Including one relapse treated later with streptomycin sulphate

+ Including one relapse treated later with streptomycin sulphate

(In the dihydrostreptomycin group one case relapsed and died after a further course and a second relapsed and survived the repeat course).

B. Use of Adjuvants

It soon became evident that one of the problems of therapy was the development of adhesions around the base of the brain with interference in the circulation of the cerebrospinal fluid. Accordingly streptokinase, a streptococcal fibrinolysin, was given in seven cases (Nos. 18, 19, 20, 23, 25, 32 and 39) with the object of lysing these fibrino-gelatinous adhesions (not wholly fibrous) occurring earlier in the disease. The articles written by Cathie (1949)[35], Cathie and Macfarlane (1950)[29] and Lorber (1951)[36] refer. Six units of the original preparation of streptokinase (Burroughs Wellcome and Co.)* were given with each intrathecal injection but no apparent benefit seemed to ensue and the impression was gained that the streptokinase caused headache, listlessness and some vomiting. In one case also (No. 39) it caused a marked pleocytosis with rise in the protein level in the cerebrospinal fluid thus masking the true picture and accordingly its administration had to be discontinued. In view of the importance of following carefully the chemistry and cytology of the cerebrospinal fluid to assess progress and watch for complications it was felt that this disadvantage of the streptokinase outweighed any possible advantages. More

* This preparation differs in strength from those in use later in which 1 vial contains 100 Cathie units or 100/6 Christensen units.

recently it has been shown that these toxic effects mentioned above are due to the hydrolysis of plasminogen by streptokinase to the actual fibrinolysing agent plasmin and not to the streptokinase itself per se or the end product plasmin (A. Fletcher (1954))[37].

Para-aminosalicylic acid (P.A.S.) was given orally later in the series of cases to those patients who had concurrent active pulmonary phthisis of adult type (cases 33, 37 and 41). It was also used in case No. 43 who was an adult with miliary lung lesions, in case No. 47 where a caseous right upper lobe pneumonia was present and in case No. 50 where there was an associated primary lung complex. This latter patient was a child who relapsed and the P.A.S. was given during the relapse. Two cases Nos. 24 and 30 did not tolerate the drug which was at that time given in fluid form only but later minor symptoms of intolerance, usually gastro-intestinal upset, were overcome by using cachets which had become available. Dosage in the adult consisted of 18 Gms. daily given three hourly in doses of 3 Gms. each and continued as long as the intramuscular streptomycin was given. Later this dosage was reduced to 12 Gms. daily and the incidence of gastro-intestinal upset lessened, evidence having been gained by many workers that the lesser dose was effective (vide discussion on para-aminosalicylic acid below). In children the dosage was 6 Gms. daily. The use of this adjuvant in this series was too sporadic to evaluate and it was only towards the end of

this series that it was decided to give P.A.S. routinely. It was believed that its use might help to improve results of therapy in all cases by synergistic action with streptomycin and furthermore prevent the development of bacterial resistance in those cases complicated by adult pulmonary phthisis. This resistance however was seldom found in tuberculous meningitis alone or in miliary tuberculosis.

Two cases Nos. 18 and 33 were treated with the protein purified derivative of tuberculin (P.P.D.) according to the method described by Smith and Vollum (1950)[26]. Case No. 18 was a child with a primary complex of the lung who developed early in the treatment of her meningitis a partial spinal block. Streptokinase was then used and the child improved temporarily and then relapsed. Streptomycin assay of the lumbar and cisternal fluids revealed that there was no diffusion of streptomycin after lumbar puncture. Intrathecal therapy was discontinued and once again the patient's condition improved temporarily. Erythrocyte sedimentation rate returned to normal and rehabilitation was instituted. Repeat lumbar and cisternal punctures revealed that the spinal block was still present and the infection was of low grade activity. After an interval of improvement however the child began to vomit and suffer from severe headaches. Early bilateral papilloedema was observed and so a developing hydrocephalus was diagnosed and the child transferred for neurosurgical investigation and treatment. Frontal burr holes were made and the lateral ventricles tapped releasing cerebro-

spinal fluid under pressure. Decerebrate fits occurred and so P.P.D. was tried in doses 0.00375 ug. increasing to 0.03 ug. given into the ventricles at two or three day intervals. The fourth, fifth and sixth doses were given into the cisterna magna. However rigors, and decerebrate fits persisted and athetoid movements developed and finally after the sixth and last injection a reaction consisting of hyperpyrexia, flushing and sweating in a conscious child developed. Death from exhaustion followed and at the post-mortem examination it was shown that this had been caused by a communicating hydrocephalus due to adhesions in the basal cisterns with in addition a block in the thoracic region of the spinal cord. The meningitis was well under control.

There was a more fortunate outcome in the second case (No. 33) who relapsed three months after discharge on to out-patient surveillance. Treatment was recommenced with the use of streptomycin sulphate by intrathecal and intramuscular routes and with oral para-aminosalicylic acid. The patient at first improved then deteriorated at the end of the third month of further therapy with signs suggesting an impending block to the C.S.F. circulation. The intramuscular dosage which had been reduced to 1 Gm. on alternate days was then increased to 2 Gms. daily and P.P.D. was given intrathecally for two weeks, on each alternate day, by gradually increasing doses at first, and then every third day for a further three weeks. Reactions to the intrathecal tuberculin, which was given by the lumbar route with the strepto-

mycin, became gross, but nevertheless slight improvement clinically and in the cerebrospinal fluid occurred. Further progress was slow and unsatisfactory so that at last all streptomycin and tuberculin treatment was discontinued and replaced by oral isoniazid (isonicotynal hydrazide). Marked improvement then took place and after three further months of treatment the cerebrospinal fluid returned to physiological levels. The dosage of isoniazid was 200 milligrams daily and this was maintained for two months following the appearance of the normal cerebrospinal fluid.

Isoniazid was also employed in case No. 46 who was deteriorating in spite of 30 weeks of intensive streptomycin therapy by combined routes supplemented also with para-aminosalicylic acid. However the patient died before the efficacy of this newer agent could be adjudged.

Neurosurgical intervention was undertaken in two cases Nos. 6 and 18 whose clinical progress has already been detailed in pages 39 (under the heading of 'clinical course during therapy') and 50 respectively.

C. General Non-Specific Therapy

In addition to the use of these agents specified above a general sanatorium type of regime was enforced, vitamins A, D and C being given orally in large dosage. Iron medication was also given and in a few cases comatose on admission a rectal drip was used. Those patients who were very ill or noisy on admission were isolated first in a cubicle ward and later, after clinical improvement transferred to the main ward, usually about the second or third

week. In those cases with active pulmonary lesions bed rest was maintained longer than in the average case, the duration being partly related to the sedimentation rate. At about the sixth week rehabilitation treatment was instituted and after cessation of intrathecal therapy the patient would be allowed up. At this stage re-education in walking was important especially in the very young child. Occupational therapy in the form of games for the children and handicraft for the adults was also instituted in the later stages of treatment as and when clinical condition permitted. To maintain morale film shows were also allowed, with cartoons for the children.

Injections both intramuscular and intrathecal were given at the times already indicated and for each intrathecal puncture special separate packs for each patient, containing needles and syringes and manometer were autoclaved. As far as possible the same person performed the punctures in the same patient and sterile masks and gloves were worn, the latter being a guard against the acquisition of streptomycin sensitivity as much as for asepsis.

In the complete periodic assessment every 2nd or 3rd week of the patient's progress the type of temperature chart with graph and list of investigations as shown in the Appendix was found to be of great help as personally it seemed easy in the management of such a protracted illness to lose sight of the overall picture.

Careful charting of any special investigations and of the results of regular weights taken weekly as soon as the patient was well enough to sit for a moment in a chair, was also carried out.

D. Length of Therapy

The duration of specific treatment is recorded below but in certain instances in survivors a period of intramuscular treatment as an out-patient is excluded. The table shows that an average of 101 - 250 days were required to effect a clinical cure thus three months therapy by combined routes at the very minimum was essential. Table IX also shows that a number of patients did not survive longer than twenty days suggesting that their condition on admission was too advanced for any treatment to be of avail. In fact each of the 14 cases in this group died on or before the thirteenth day.

Table IX - Duration of Specific Treatment

Number of Days	Alive	Dead	Total
1 - 20	0	14	14
21 - 50	1	5	6
51 - 100	1	4	5
101 - 150	4	4	8
151 - 200	5	0	5
201 - 250	4	4	8
251 - 300	2 *	2 *	4
301 - 350	1 *	0	1
350 and over	1 *	0	1

* 1 case within each group includes also treatment duration for a relapse or recrudescence of disease.

Complications following Therapy

The commonest complications in the survivors were either bilateral nerve deafness, vertigo or both which signs were related to the type of antibiotic employed. Of the 19 patients alive after treatment, nine had a bilateral nerve deafness, two having been treated with the calcium chloride complex of streptomycin and seven with dihydrostreptomycin, two of the latter suffering only slightly. In addition one patient who eventually died (No. 46) also developed deafness after treatment with dihydrostreptomycin and therefore this would raise the total to eight out of twenty-nine cases treated by the latter developing this complication whilst only two out of a total of sixteen cases treated by calcium chloride complex were affected.

Vestibular upset was noted in four survivors, two being treated by the calcium chloride complex and two by the dihydrostreptomycin but the vertigo was not so troublesome to the patient as compensation appeared to occur over the course of a few months.

In the few cases including relapses treated with streptomycin sulphate no nerve deafness or vertigo was observed.

The complications following therapy have already been mentioned in respect of cases Nos. 6 and 11. Case No. 17 had a metatarsus varus on walking again following cure of her relapse of meningitis and this deformity was corrected under orthopaedic supervision. Case No. 35 developed later a

small gland in the neck which formed a cold abscess and eventually resolved under further streptomycin treatment. An organism of bovine strain was isolated from the pus obtained and it was still streptomycin sensitive. Her meningitis was also due to the bovine strain which had been isolated on culture.

Finally, two cases (Nos. 34 and 51) exhibited abnormal behaviour after completion of therapy. They were both children and this misbehaviour was manifested by extreme naughtiness, screaming fits and terror starts and in the former instance persisted for some months. Their behaviour resembled that which sometimes occurs in a post-encephalitic patient. Eventually both recovered from this abnormality.

Methods and Detail of the Follow-up

The length of the follow-up of the survivors of this series varied from one year to four years and eleven months, the condition on the 31st December 1953 being the final assessment for this paper. This period of follow-up is based on the fact that a minimum period of two years is really advisable in order to assess results of treatment because of the danger of a late relapse.

The follow-up period commenced after the discharge of the patient from hospital and consisted of a first period during which intramuscular streptomycin was still given daily. The case was readmitted every fortnight for two days for assessment and further diagnostic lumbar puncture. If progress was satisfactory the period at home was increased to

one month. After 8 - 12 weeks on the fortnightly pattern the patient would then attend the out-patient clinic at monthly intervals and eventually the frequency of these visits would become less if the patient remained well. In addition the family doctor and the parents or relatives were warned that the patient was to be sent for readmission immediately, should any illness or pyrexia develop, even if minor.

During these revisits, whether as in-patient or out-patient, a complete physical examination including chest X-ray, ophthalmoscopy, and check of auditory and vestibular function by the otologist was carried out. When the patient was admitted a full cytological and chemical analysis of the cerebro-spinal fluid was made with bacteriological examination of films, and with inoculation of culture and guinea-pig. A rough psychometric assessment was performed by enquiry about school progress reports in children, ability to carry out their occupation in adults and the alertness and development of infants under school age. Perhaps this assessment of the quality of the survivors could have been made more accurate by the employment of the Gisell-Stanford Binet tests for pre-school age, the Terman-Merrill for older ages, and the Collins-Drever for deaf children as is described by Illingworth and Lorber (1950)[38]. The impression was gained that some of the children were more alert and intelligent after recovery from the meningitis than before (e.g. cases Nos. 17, 20, 23, 35 and 40).

Details of the length of the follow-up period with the condition of the patient on 31st December 1953 are set out below.

Table X - Length of Follow-Up and Condition on 31st Dec.1953

Case Number	Auditory Upset	Vestibular Upset	Calcium Chloride Complex of Streptomycin	Dihydrostreptomycin	Streptomycin Sulphate	Condition on 31.12.53	Follow-Up in Months
1	+	+	+	-	-	Vertigo compensated but falls in the dark: Hearing improved. Has had a child: Physically and mentally well.	59
5	+	slight	+	-	-	Alive and well. Rides bicycle. Roller skates.	53
6	+	-	+	-	-	Spastic lower limbs. Nerve deafness. Left upper lobectomy.	53
11	-	-	+	-	-	Bilateral apical tuberculosis with cavitation. Resistant organism. Died 16.12.51.	28
17	slight	slight	-	+	-	Alive and well. Good school report. Metatarsus varus.	32
20	+	-	-	+	-	Alive and well. Passed Grammar School Entrance Exams. Does P.T. and swims.	35
22	+	slight	-	+	-	Alive and well. Drives van. Is very alert.	35
23	-	-	-	+	-	Alive and well. Good school report. Swims.	35
33	+	slight	-	+	+	Condition satisfactory: Still rather weak.	12
34	+	-	-	+	-	Behaviour disorder. Physically well. Attends school for deaf.	27

Cont'd.

Case Number	Auditory Upset	Vestibular Upset	Calcium Chloride Complex of Streptomycin	Dihydrostreptomycin	Streptomycin Sulphate	Condition on 31.12.53	Follow-Up in Months
35	-	slight	-	+	-	Top of class in all subjects for 2 years. Cold abscess in neck. Occasional headaches.	27
38	-	-	-	+	-	Alive and well physically and mentally.	25
39	-	-	-	+	-	Phycically and mentally well.	26
40	slight	-	-	+	-	Physically and mentally well. Very good school report.	23
41	slight	-	-	+	-	Married and has a child. Recovered from relapse of pulmonary tuberculosis.	24
45	-	-	-	-	+	Physically and mentally well.	17
47	-	-	-	+	-	Calcification and bronchiectasis in right upper lobe (tuberculous). Otherwise alive and well.	27
50	-	-	-	+	+	Physically and mentally well.	12
51	-	-	-	-	+	Behaviour upset temporarily Eventually physically and mentally well.	18

N.B. Auditory and vestibular function was in each case assessed with the aid of audiograms and labyrinthine function tests.

The cerebrospinal fluid returned to within normal limits, as have been defined, in 15 out of the 19 cases surviving. Normal levels in the majority of patients were reached within three to ten months, first the sugar, then the chloride, then the cell count and lastly the protein values in that order becoming within the physiological limits. The protein value often remained raised along with a slight increase in cell count for a considerable period - even up to six months following the appearance of the normal sugar level in the cerebrospinal fluid[24].

In case No. 45 where a diagnosis of a simple serous tuberculous meningitis was made, the fluid became normal in six weeks.

In four cases abnormalities persisted, in three the cell count remaining slightly raised and in the fourth the protein being on the high side. The sugar and chloride values, however, in all four remained normal.

Relapses and Recrudescences

Cases in which the disease appeared to recur after marked improvement or cure, were defined as recrudescences or relapses as described by MacCarthy and Mann (1950)[24]. A relapse was considered to have occurred when the patient had remained well without treatment for a definite period and the cerebrospinal fluid had returned to normal whereas a recrudescence occurred whenever therapy was discontinued although the cerebrospinal fluid might have approached normality.

Three cases relapsed within the above definition,

case No. 17 four months after discharge from all treatment, case No. 33 five months afterwards and case No. 50 three months afterwards. All these cases responded satisfactorily to a further full course of treatment, dihydrostreptomycin being used for No. 17, dihydrostreptomycin with streptomycin sulphate for the relapse in No. 33 and calcium chloride complex and then the sulphate of streptomycin in No. 50.

Case No. 27 was classified as a recrudescence and deterioration took place at the end of a second rest period when all therapy had been discontinued. Up till this time, the child had improved, raised temperature had settled, weight was being gained and the cerebrospinal fluid was within normal limits except for a slight increase in the number of cells per cubic millimetre. Treatment had to be resumed with dihydrostreptomycin using intensive intrathecal therapy but the child died. A pulmonary miliary tuberculosis was also present.

Signs and symptoms of relapse or recrudescence in each of these four cases were headache, pyrexia and a personality change towards irritability. Symptoms usually appeared first followed by changes in the cerebrospinal fluid and lastly signs of meningeal irritation reappeared.

Miliary Tuberculosis and Tuberculous Meningitis

Most of the points mentioned below have already been presented in various parts of the analysis above but for convenience are once again summarised together under this heading.

10 cases in this series suffered from both types of tuberculosis and they all died in spite of the meningitis being

in the early stage in five, the intermediate in four, and the late stage in one.

Six of the ten cases were found to have a meningitis and pulmonary miliary disease on admission. The other four cases were already known to have suffered from the latter and developed the meningitis as a complication. In two of these cases the meningeal infection appeared after apparent cure following a course of intramuscular streptomycin for several months. In the two other cases the meningitis developed during the intramuscular treatment and, as has been emphasised, the striking feature was its insidious onset. In case No. 30 increase in headache, pyrexia and irritability were the only changes noted there being no neurological signs on examination.

Case No. 46, a patient with miliary disease developing meningitis died in spite of radiological clearing of the lung confirmed by autopsy. The radiological picture in case No. 21 also cleared but active lesions were seen at post-mortem examination. In case No. 24 improvement in the chest picture occurred but nevertheless death ensued.

These examples stress the fact that intramuscular therapy alone is not sufficient to control tuberculous meningitis and further that the progress in the chest picture is not always a guide to prognosis.

The above ten patients included four who had in addition miliary lesions scattered throughout other viscera in the body.

Summary of the Results of Treatment

Out of 52 unselected cases of tuberculous meningitis 19 survived this including two patients presumed to have a serous tuberculous meningitis.

The majority of the survivors were over the age of three years if considered as a percentage of the total in the series under and over this age. Thirty-three of these cases had tuberculous chest lesions confirmed radiologically and in ten miliary lung disease was present. All the latter died. Bacteriological or post-mortem confirmation of diagnosis was present in 45 out of the 52 cases. Nine cases developed a block in the cerebrospinal fluid circulation and three patients relapsed. One patient died after a recrudescence of disease.

Calcium chloride complex of streptomycin was used for treatment in 16 cases, streptomycin sulphate in 4, and dihydrostreptomycin in 29 cases. The intrathecal and intramuscular routes were used. Streptokinase, 6 units per intrathecal injection was given in six cases without apparent benefit, para-aminosalicylic acid was used in six cases, protein purified derivative of tuberculin in two cases and isoniazid in one case. Neurosurgical intervention was carried out in two patients.

Length of follow-up varied from 59 months to 12 months. Eight out of the 29 cases treated by dihydrostreptomycin developed nerve deafness and only two out of 16 treated by the calcium chloride complex - or taking survivors only, seven out of 12 treated by the former as compared with two

out of 5 by the latter. The cerebrospinal fluid in 15 out of the 19 survivors returned to normal on an average within five months from the onset of therapy.

DISCUSSION

Having analysed carefully in detail these 52 unselected cases of tuberculous meningitis, let us now turn to the examination of results obtained by other treatment centres. In this series just described the mortality has been shown to be 63.5% and therefore two out of every three patients were dying leaving much room for improvement. We soon find on reviewing the literature on results of therapy that there are many different survival rates reported with improved figures in the later years as more experience was gained. We also find a great diversity of detail in therapeutic measures and in the use of differing antituberculous agents and therefore it is proposed to consider these varied regimes and decide what appears to be the most advisable type of therapy. Finally it would be valuable to review future prospects in view of the effective newer antituberculous agents now available.

Table XI below lists briefly the results reported by many centres.

Table XI - Results in Treatment of Tuberculous Meningitis

Source	Total No.of Cases	Survivors off Therapy	Remarks
Regime: Intrathecal and intramuscular streptomycin			
1948, Debré et alia - French series[39]	93	35(38%)	
Frontali[29]	98	30(31%)	Normal CSF - 30
Orrego[29]	38	12(32%)	
Mann[40]	33	5(15%)	Interrupted regime

Source	Total No. of Cases	Survivors off Therapy	Remarks
1949			
Todorovic - Yugoslav series[41]	287	82(28.5%)	
Fouquet et alia[42] French series	147	43(29%)	
Bernard et alia[43] French series	100	22(22%)	
Dubois et alia[44] Belgium series	83	38(46%)	
Hooft et alia[45] Belgium series	50	8(16%)	
Fornera[29]	24	10(38%)	Normal CSF - 6
Scottish Streptomycin Subcommittee Trials[23]	81	20(38%)	Selected cases
Capon and Todd[46]	55	7(12%)	
1950			
Ariztia et alia - Swiss series[47]	43	20(46.5%)	
Veterans Administration[48] United States Forces American Series 1	81	9(11%)	
Veterans Administration[48] United States Forces American Series 2	140	30(21.4%)	
Medical Research Council[49]	369	104(28%)	
Cairns, Smith and Vollum[50]	60	30(50%)	
Cathie and Macfarlane[29] - Series A	20	5(25%)	Normal CSF - 4
MacCarthy and Mann[24] - Series A,B and D	37	14(38%)	Normal CSF - 8
1951			
Illingworth and Lorber[38]	82	36(43.9%)	Early cases selected
Lorber - Series A and B[36]	67	29(44%)	
Calnan et alia[51]	54	16(30%)	Series includes 10 treated on IM streptomycin only
1952			
Naismith - Series 1[52]	26	13(50%)	
Robertson[53]	146	69(47%)	
1953			
Smith[54] - Series A	80	42(52%)	Includes cases in ref.no.50
Russell and MacArthur[55,56]	33	12(36.3%)	
Present series	52	19(36.5%)	6 cases treated also with PAS

Source	Total No. of Cases	Survivors off Therapy	Remarks
Regime: Intramuscular Streptomycin only			
1948 Mouriquand[57]	45	25(55.5%)	Short follow-up.
Medical Research Council[25]	28	3(11%)	
1949 Rubie and Mohun[27]	10	2(20%)	
Levinson[58]	33	10(30%)	
MacCarthy and Mann[24] - Series C	6	0	
Capon and Todd[46]	28	3(10.7%)	
Regime: Intramuscular and intrathecal streptomycin with streptokinase			
Cathie[35] - Series B	19	11(58%)	
Regime: Intramuscular and intrathecal streptomycin with streptokinase and a sulphone			
Cathie and Macfarlane[29] - Series B	40	23(58%)	Normal CSF - 7 6 cases - no sulphone
Regime: Intramuscular and intrathecal streptomycin with a sulphone			
1950 Veterans Administration[48] United States	62	8(13%)	
1953 Lincoln and Sifontes[28]	52	35(67.3%)	
Regime: Intramuscular and intrathecal streptomycin with sulphone and PAS			
1950 Cocchi and Pasquinucci[22] Italian series Group 1	57	12(21%)	Normal CSF: 10
Group 2	66	30(45.5%)	29
Group 3	60	37(61%)	33
Group 4	40	34(85%)	32
Group 5	44	34(77%)	25
Total	267	147(55%)	129

Source	Total No. of Cases	Survivors off Therapy	Remarks
Regime: Intramuscular and intrathecal streptomycin with PAS			
1950 Veterans Administration[48] United States	28	13(46%)	
1952 Naismith[52] - Series 2A and 2B	65	44(67.7%)	
Jamieson[59]	35	28(80%)	
1953 Bulkeley[60] - Series 1	31	18(58%)	
Regime: Intramuscular and intrathecal streptomycin with tuberculin			
1950 Choremis et alia[61] - Greek series	132	81(61.4%)	Intravenous tuberculin
1953 Smith[54] - Series B	37	22(59%)	Intrathecal tuberculin in unfavourable cases.
Regime: Intramuscular and intrathecal streptomycin with isoniazid			
1953 Anderson et alia[62]	7	7(100%)	Follow-up brief. Series too small
Torres-Gost[63]	100	34(34%)	60 of 94 survivors still on therapy
Regime: A.C.T.H., isoniazid, intramuscular streptomycin and PAS			
Bulkeley[60]	31	25(80.6%)	13 out of 31 cases on A.C.T.H. and isoniazid only

The above table is interesting in that a study of these principle series reported shows a gradual improvement in the results obtained since streptomycin therapy was first inaugurated. Although the number of series reported later in each different regime grouping is not sufficient perhaps for statistical comparison certain trends can nevertheless be noted. In the group in which the treatment was streptomycin by intrathecal and intramuscular routes the average percentage survival rate rises gradually being 29% in 1948, 29.2% in 1949, 31.3% in 1950, 39.3% in 1951, 48.5% in 1952 and 41.6% in 1953. Of course many factors have to be considered in this comparison of results these factors being improvement in early diagnosis, the age groups, the use of neurosurgery in selected cases, the dose of streptomycin employed, the use of interrupted or continuous regimes, the duration of therapy, the type of streptomycin and the length of follow-up. These points shall have to be discussed below.

Treatment using streptomycin by the intramuscular route only (average survival rate 22.9%) may be briefly mentioned here as it can be dismissed readily from discussion. In spite of the fact that bacteriostatic levels of streptomycin can be obtained in the cerebrospinal fluid by intramuscular therapy alone, these levels being higher the more advanced the stage of disease, it was exceptional to get a satisfactory clinical response[25]. This method of therapy was rapidly abandoned in this country following the poor results obtained in the first number of cases so treated, as exemplified by

the series reported by the Medical Research Council, Rubie and Mohun and MacCarthy and Mann as shown in the table. The results obtained by Mouriquand have not been confirmed by other workers and in the article referred to in the table the period of follow-up was brief and was not detailed. Many Americans when streptomycin first appeared were rather chary of using the drug intrathecally, due no doubt to the toxic effects that arose from the less pure preparations used at that time and partly from the larger doses employed. One author went so far as to state dogmatically that he considered streptomycin should never be used intrathecally and in 1949 there were still some who considered the intrathecal route dangerous. It was thus that Cairns, Smith and Vollum[50] in reporting their experience in therapy in the United States in 1950 warned against this concept. Indeed the fact that cases of pulmonary miliary disease can develop tuberculous meningitis whilst under treatment with intramuscular streptomycin (cases 30,46) is sufficient warning that this route alone should never be employed (if streptomycin is the only antituberculous agent being given).

When we next examine the results obtained, using in addition to streptomycin by combined routes, adjuvants we find further improvement in survival rates (average 58.3%) but because of the multiplicity of drugs and methods employed, it is often difficult to assess whether this improvement is due to the one or many additions. Reviewing these series in which adjuvants are displayed it would seem that the

addition of para-aminosalicylic acid was favourable and more so than the toxic drugs of the sulphone group. The appearance of isonicotynal acid hydrazide (average survival rate 73.8%) promises an even better line of therapy but as yet there has not been time for reports of results of treatment in sufficient numbers of cases with adequate follow-up periods.

We shall now proceed to examine in turn each of the various agents or methods employed in treatment and in so doing will realise the importance and value of carefully conducted trials in evaluation of therapeutic measures in a disease as chronic as tuberculous meningitis and as prone to relapse after lengthy therapy.

Use of Streptomycin

"Il faut frapper très vite, mais ne pas frapper trop fort" - Loffler (1948)[64]

Since the discovery of streptomycin by Waksman and his associates this antibiotic has been, until recently, the mainstay in the treatment of tuberculous meningitis. As has already been mentioned, it was soon found that administration by intramuscular route alone, although giving 8 µg. streptomycin per cubic centimetre (cc.) of cerebrospinal fluid[55] within four hours of injection, was unsatisfactory and indeed in patients under the age of three years disastrous[25], and therefore the standard practice has been to give the combined course using intrathecal and intramuscular routes. Clinical experience in treating cases soon pointed

out that prolonged therapy was necessary and this fact was emphasised by the number of cases who relapsed during the follow-up period. The incidence of the relapse rate within the first six months from cessation of therapy was highest and then gradually fell up to a year. After twelve months survival the prognosis became brighter with danger of relapse still present but more remote[65]. Accordingly most authorities at first favoured a minimum of three months continuous therapy but now incline towards a more prolonged course up to six months.

Intramuscular dosage employed at first for adults varied from 1 - 3 Gms. daily given in three-hourly divided doses but the incidence of toxic signs of albuminuria, haematuria and cylindruria with nausea and vomiting was high. The guinea-pig experiments of Feldman, Hinshaw and Karlson (1947)[66] and trials of streptomycin in pulmonary tuberculosis by Barnwell, Bunn and Walker (1947)[67] suggested that smaller dosage at less frequent intervals was equally effective and when this was tried in the therapy of tuberculous meningitis the incidence of these toxic effects fell without any reduction of the efficacy of treatment. The current practice of most clinicians is still to follow the intramuscular dosage schedule as recommended in the Medical Research Council (M.R.C.)[25] trials in 1948 and that is to calculate the dosage on the scale as used in this series and described in the analysis under streptomycin therapy up to a maximum of 1 - 2 Gm. daily.

More recent experience in pulmonary tuberculosis has

suggested that streptomycin 1 Gram (Gm.) intramuscularly twice weekly[60,68-70] may be as effective as the daily dose, this time interval being related to the growth and multiplication of the bacterium but recent trials in which the use of isoniazid with different schemes of dose of intramuscular streptomycin were compared, showed a higher incidence of bacterial resistance in the group in which the twice weekly rather than the daily dosage was given. However no series have as yet been reported regarding the use of this regime in combination with intrathecal therapy in tuberculous meningitis and considering the different problems presenting in the latter disease one doubts if the less intensive method would be as effective or safe.

Whereas the intramuscular regime suggested by the M.R.C. in 1948[25] (i.e. 0.02 Gm. per pound body weight per day) has been widely employed there was much more variation in the concurrent intrathecal dosage. This latter varied greatly in minor detail and fell into two main groups the interrupted and the continuous schedules. The M.R.C. advised the interrupted method and considered that the best results were obtained with as little intrathecal treatment as possible with frequent and relatively longer rest periods off therapy (I.T.) They however modified this view later. Cathie and Macfarlane (1950)[29] recommended a short course of twenty-four intrathecal injections and a Liverpool series[72] also favoured short interrupted courses.

Mann (1948)[40] amongst others has considered that

patients, especially children, have benefited from frequent rest periods with improvement in mental and physical well-being and with less incidence of nausea and vomiting, but one's own experience would suggest that any rest interval off therapy before, at the very least, the sixth week on treatment, is unwise. Indeed case No. 27 deteriorated at the first rest interval allowed after three months continuous treatment and in this series it is the latter schedule that has been favoured. One also noted that it seemed to upset the children more when therapy had to be resumed and therefore it was kinder to employ a dosage with later, gradual decreasing frequency in intrathecal injections, this in itself being an encouragement to the patient that he or she was getting better. Illingworth and Lorber (1951)[38] noted that deterioration occurred within the first rest period if this was, as often advised, about the fourth week and Debré (Paris), Dubois (Brussels) and Cocchi (Florence)[73] all favoured uninterrupted and prolonged treatment. A later report of the Medical Research Council[49] recommended more intense intrathecal therapy the number of days of the latter being at least 50% of the duration of the intramuscular course, and a study of 350 cases in a report by the Ministry of Health (1950)[74] advised that intrathecal treatment should be at least 75% of the intramuscular course and reported improved results. Sommer (1950)[75] confirmed this but warned that intrathecal streptomycin may precipitate blocks to the cerebrospinal fluid circulation.

In fact the general trend of intrathecal and intramuscular therapy from the earlier years has been towards less intense daily dosage but more prolonged treatment.

Choremis (1950)[61] advises that one should commence with a small intrathecal dose and then gradually increase to the maximum tolerated short of producing toxic signs and he stresses that this is especially important in advanced cases as he believes that a large initial dosage might cause a greater reaction intrathecally and thus hasten death. This method, however, has not been generally employed.

Dubois et alia (1949)[44] treated six patients by the intrathecal route alone but the results were unsatisfactory and all died.

In this series the form of the intrathecal therapy has already been described in the analysis under streptomycin treatment. Briefly after twelve weeks combined therapy with a short initial intensive intrathecal course rest periods were instituted and then the treatment gradually tailed off according to clinical evaluation at each rest interval. This latter emphasises the point, which bears repetition, that no matter whether continuous or interrupted schedules are employed treatment for each individual case has to be judged on individual merits. The impression on reviewing this series was that there was a tendency to undertreat intrathecally and probably initial therapy of daily injections should have been prolonged up to fourteen days in more cases, with a higher dosage in children as they require weight for

weight relatively larger doses than adults[71]. Cairns, Smith and Vollum (1950)[50] advise one to overtreat rather than undertreat. A consideration of the reports on the different therapeutic regimes using streptomycin by combined routes would suggest that a minimum of six months intramuscular therapy on a dosage of 0.02 Gm. per pound body weight per day up to 1 - 2 Gms., and at least three months continuous intrathecal therapy on a dosage of 0.05 to 0.1 Gm. (graded according to age) in 5 - 10 ccs. normal saline per injection should be employed, giving approximately 45 injections as a minimum. Then after the three months intrathecal dosage a gradual reduction in the frequency of the latter with intermissions of rest periods can be safely employed[71]. The mere existence, however, of such a large variety of minor details in intrathecal therapy would suggest that treatment initially with or without rest periods does not greatly alter the survival rate in favour of one or the other routine.

Whilst on the subject of intrathecal therapy it is worth stressing a few details in technique. It is undoubtedly of advantage for the same doctor to perform the lumbar punctures in the same patients and at the same time of day this latter being at midday from the point of view of maintaining as high a level of streptomycin in the cerebrospinal fluid as possible. The former item was emphasised by Cocchi and Pasquinucci (1950)[22] and by Sir H. Cairns (1949)[76] as thereby the possibility of trauma and the obtaining of bloodstained fluid is lessened, the doctor being more familiar with the

best intervertebral space to choose and the correct direction and angulation for the needle. Furthermore, expertly performed each lumbar puncture should cause little or no pain and in children apprehension and future resistance and difficulties are thus obviated. One's custom in this series was for each patient to have his or her own batch of streptomycin and sterile packs of needles, syringes and manometer sterilised by autoclaving. (Minkenhof et alia (1948)[77]). Whilst the streptomycin was being injected it was admixed well with the cerebrospinal fluid. Sterile masks were worn at lumbar puncture and also rubber gloves for the reasons which have already been mentioned. (The subject of streptomycin sensitivity and desensitisation will be mentioned again below under toxic effects of the antibiotic).

Toxic Effects of Streptomycin and Dihydrostreptomycin

In this series toxic effects that could be attributed directly to the streptomycin were negligible except for an incidence of vertigo and/or deafness, the latter being more frequent in those patients treated with dihydrostreptomycin. Toxic reactions, that have been described, fall into four main groups (Farrington et alia, 1947)[78]:-

(a) Histamine group - this is manifested by flushing, headache, and a fall in blood pressure and these are due to impurities in the drug and have been abolished by use of the purer preparations and with treating streptomycin with histaminase (McDermott, 1947)[79].

(b) Anaphyllactoid group - this is characterised by skin rashes frequently ephemeral, conjunctivitis, leucocytosis, oedema, eosinophilia and pyrexia. The pyrexia usually appears after the 10th - 18th day of therapy and the rashes, either with, or without, fever, later at the second to third week. The rashes may be morbilliform, blotchy, maculo-papular and/or pruritic and are often accompanied by peri-orbital oedema, superficial scaling of the skin, and enlarged lymph nodes. An exfoliative dermatitis has also been described as due to streptomycin. Accompanying these rashes may be headache, nausea, vomiting and joint pains.

These anaphyllactoid reactions are probably also related to impurities and are reduced by use of purer preparations. If these reactions are severe therapy would have to be discontinued and desensitisation carried out.

Sensitisation to streptomycin can not only occur in the patient but in the doctor or nurse administering the drug[80]. A dermatitis in four out of 80 nurses exposed to risk was described in 1948 by Crofton and Foreman[81]; four cases of epidermal sensitisation were also described in 1947 by Strauss and Waring[82] and further cases by Stringfellow (1948)[83] and by Rauchwerger et alia (1948)[84]. Within one's own experience during the time period of the above series one sister and one nurse both became sensitised. The rash in both cases was typical of that described in the above-mentioned reports and was a pruritic papular erythema on the antecubital fossae, on the fingers and around the eyes accompanied by periorbital

oedema. This condition can be very disabling and therefore a method of desensitisation as described by Crofton (1953)[85] is welcome. Desensitisation in patients is fortunately easier than in the medical attendants. In both cases instanced above removal from danger of contact was practical and was carried out but this fortuitous result is not always so easy. Therefore nursing and medical staff who have positive patch tests to streptomycin would be well advised to wear rubber gloves when handling this antibiotic.

(c) Renal group - As streptomycin is excreted entirely through the kidneys, one finds high concentrations in the urine. Cathie (1948)[86] found 500 - 1,000 units of streptomycin per cu.mm. in the urine (1 unit ≡ 1 µg. streptomycin) even after one daily injection, Cooper and Cohn (1948)[87] found 41% - 80% of the total dosage was excreted in twenty-four hours, the National Research Council (1946a)[86] reported 60% - 80% of one injection to appear in the urine within twenty-four hours and Russell and MacArthur (1950)[55] said that they found 320 - 3,200 µg. per millilitre in the twenty-four hour urine sample after the usual average daily intramuscular and intrathecal dosage. Therefore it is not surprising that on high dosage there is a renal group of toxic reactions, these being albuminuria (usually slight), haematuria and casts which are more numerous if the urine is acid. Some slight impairment of renal function occurs on high dosage and recovery will ensue even if streptomycin therapy is continued.[79] However there follows from this, that one should in the presence of

marked renal impairment modify one's dosage of streptomycin. In a New York series of cases[79] a high incidence of toxic signs resulted (1) if the dosage was high (2) if the dosage was moderate and kidney damage was present and (3) if intrathecal dosage was employed. A case of fatal toxic encephalopathy due to streptomycin is reported by Hunnicult et alia (1948)[88] and the causative factor here was poor renal function.

(d) Neurotoxic group - These are the most important of the four groups of reactions and consist mainly of vertigo and nerve deafness. Associated with the former may be headache, dimness of vision, a transient numbness around the lips, nausea, vomiting and nystagmus. The first symptoms are usually those of dimness of vision in the evenings and the headache which may last only twenty-four hours. This occurs about the sixth week if the dosage is 1 Gm. streptomycin intramuscularly per day and the third week if 2 Gms. daily (Crofton et alia (1951))[89]. With the additional intrathecal therapy the time of onset is usually about the 3rd - 4th week on dosages such as employed in this series. A lateral nystagmus may or may not accompany the vertigo or alternatively may alone be present. Symptoms may be acute at first and subside after a week, then there is a period of latent vestibular dysfunction for six to eight weeks and finally compensation occurs. In those cases affected to a less degree it is usually a sudden movement of the head whilst the patient is turning in bed that produces the vertigo and first draws attention to it. Labyrinthine function tests show that the vestibular defect may recover or

persist in which case fortunately as the patient becomes ambulant compensation occurs by day and unsteadiness of gait only troubles at night. This toxic manifestation is therefore not too troublesome to the patient recovered from tuberculous meningitis.

A bilateral nerve deafness can also occur, and may be of quite late onset (Sher, 1951)[90]. This is preceded by a low pitched tinnitus and the earliest loss is usually a high tone deafness[90,91] although Brown and Hinshaw (1946)[92] found the reverse. There is no compensation for this hearing loss and so it is a much greater handicap to the patient and indeed to infants who have not yet learnt to speak. Dihydrostreptomycin is the main offender in causing deafness although less toxic to the vestibular apparatus. In this present case series the only serious toxic manifestations encountered were those of vertigo and deafness and the follow-up revealed the latter as the more incapacitating. Dihydrostreptomycin was employed for treatment in the majority of cases but this limited experience would suggest that weight for weight it did not seem to be any more effective than the calcium chloride complex of streptomycin for whom it had been substituted and it resulted in the more serious toxic effect.

The last cases in this series were treated with streptomycin sulphate which is 95% pure and this preparation appeared to be the most satisfactory salt of the whole group of streptomycin drugs.

Further toxic manifestations occurring rarely and mentioned by McDermott (1947)[79] are leucopenia and relative granulocytopenia. One reported case developed thrombocytopenic purpura on a daily dose of 6 Gm. Cocchi and Pasquinucci (1950)[22] believe that large amounts of streptomycin interfere with immunity development.

The streptomycin drugs also have a local irritant effect which seems to be related to impurities as they occur to a much less extent when the more purified preparations are used. One of these effects is pain on intramuscular injection. The other local irritant effect is exhibited on intrathecal administration in a person with a normal C.S.F. The latter shows a marked rise in cell count, predominantly polymorphonuclear in type, and in protein level which subsides rapidly and should be normal within one week. Streptomycin is poorly tolerated intrathecally if there is no meningeal reaction[86]. The irritant effect of streptomycin is demonstrated further by the frequent development of root pains on injection and by an erythema of the cord and thickening of the leptomeninges at the site of injection[55]. If streptomycin is given in too large dosage, especially if by cisternal or ventricular route, convulsions, coma and hyperpyrexia may follow. If the excessive dosage is not so great, however, somnolence and urinary retention appear for a time after injection.

When the streptomycin is injected intrathecally there occurs in the patient with tuberculous meningitis, a typical reaction, in addition to that due to its mild irritant effect.

This reaction is characterised by high value spikes in cell count and protein readings following each intrathecal injection and most marked in the early days of therapy. These spikes gradually become less pronounced over a period of three to four weeks and this pattern, considered to be pathognomonic of tuberculous meningitis, is shown well in many of the graphs of the behaviour of the C.S.F. constituents during therapy which are found with the case records in the Appendix. This picture, for example, is not seen in a haemophilus influenzae meningitis where the levels gradually subside to normal and Smith and Vollum (1950)[26] believe that these spikes, where ratio of polymorphs to lymphocytes increases, are due to the release of breakdown products of the tubercle bacillus which has been affected by the streptomycin. Thus the latter has two effects intrathecally, one associated with a mild irritation and one with a therapeutic action.

On combined intrathecal and intramuscular therapy it has been proved that diffusion into and throughout the cerebrospinal fluid is satisfactory and bacteriostatic levels can be maintained, these levels being higher if the meninges are inflamed. However very little streptomycin diffuses into the brain tissues and this is a disadvantage should the source of the meningitis be a tuberculoma sited in the depth of a deep sulcus.

At first there was some debate as to whether the neurotoxic reactions were due to the streptomycin and/or its impurities associated with it or to the tuberculous meningitis

process itself. However if this antibiotic is used in non-meningeal forms of tuberculosis or in non-tuberculous infections[93], these reactions still do occur and furthermore, if the administration of the antibiotic is stopped when these toxic manifestations appear, these toxic signs may disappear and will reappear on resumption of therapy. If the treatment is not too prolonged, as for example in a non-tuberculous infection deafness may appear to recover, although this is not confirmed by audiograms.

The reason for this apparent selective toxic reaction of streptomycin on the cochlear and vestibular apparatus is difficult to explain and there is no convincing supporting histological evidence of their damage or involvement. Nevertheless Stevenson et alia (1947)[94] described five cases treated with streptomycin, four of which had suffered from tuberculous meningitis, in which a liquefactive necrosis was found in the cells of the ventral cochlear nucleus in all five and in the inferior vestibular nucleus in two - both meningeal cases. On the other hand, Baggenstoss et alia (1947)[95] reported active tuberculous involvement of the eighth nerve and Professor Ormerod[69] demonstrated tuberculous infiltration of the cochlear portion in a streptomycin treated deaf patient who had had a tuberculous meningitis. Illingworth and Lorber (1951)[38] also noted that very few non-meningeal tuberculous cases treated with streptomycin develop deafness but the weight of evidence and the majority favour a specific neurotoxic action of the antibiotic itself. In fact Floberg et alia

(1949)[96] showed that streptomycin inhibited intracellular reproduction of nucleic acids and this action appeared to be electively bound to the nerve cells of the vestibular pathway.

With the evidence as described above of all these toxic signs, the commoner ones of which in order of frequency are fever, vertigo, rashes, vomiting, deafness and nephritis[23], it is therefore desirable to select a preparation of streptomycin that is less likely to give rise to troublesome side effects. The dihydrostreptomycin salts, the hydrochloride and the purer sulphate are excluded by their causing, as we have seen, a higher incidence of deafness[52,90,97-105] and by the fact that they are no more efficacious although less painful on intramuscular injection[89,106-108]. Of the streptomycin salts, the sulphate is the purest, is very efficient and is less irritant than the double salt calcium chloride complex and the hydrochloride, and therefore the sulphate should be used routinely. Furthermore it mixes better than some of the other salts with streptokinase should one wish to use the latter adjuvant to therapy - of doubtful value. If a change in intrathecal therapy from use of the calcium chloride complex of streptomycin to dihydrostreptomycin or streptomycin sulphate is made, the precaution of allowing a few days interval between injections should be observed as these preparations do not mix and cause precipitation. With daily intramuscular dosage it may be better not to exceed in the adult more than 1 Gm. daily - that is less

total daily dosage than the factor 0.02 Gm./lb./day, which should be reserved for children, would allow - as several reports have shown that toxic effects increase proportionately to rises of the daily dose to 2 Gms. and 3 Gms. daily respectively[67,68,89,93]. Intrathecal dosage probably should not exceed 100 mgms. daily.

If hypersensitivity reactions are encountered it may be dangerous to continue therapy without desensitisation and antihistamine therapy. Continuation of therapy may result in severe liver damage or anaphyllactoid shock. One such case of severe shock is reported by Rosen (1948)[109]. Neurotoxic signs, as above, do not indicate necessity for cessation of therapy but when these and other toxic manifestations are present especially on moderate dosage, renal function should always be checked.

Use of Adjuvants

The overall survival rate as shown in table XI for cases treated with streptomycin by combined routes was 34.4% and this left much room for improvement. Accordingly other antituberculous agents were sought for possible use in meningitis and could be classified into three groups: in the first group one might consider the thiosemicarbazones, the sulphones of which the active principle is diaminodiphenylsulphone (D.D.S.), and para-aminosalicylic acid. These drugs appeared to act synergistically with streptomycin and also to lessen the incidence of bacterial resistant strains. For the latter reason they were tried concurrently with streptomycin in

pulmonary tuberculosis especially, and for the former reason have been employed in meningitis, resistant strains being rarer[25,110]. (Only two cases both with lung infections in this series developed bacterial resistance as has already been noted). This problem of resistance is an interesting one and recent work has shown that the antibiotic appears eventually to become an essential nutrient for the organism[111].

The second group of drugs for consideration are those employed to try and reduce or overcome the formation of adhesions, one of the main causes for unsuccessful therapy. These drugs are (1) protein purified derivative of tuberculin (P.P.D.) (2) streptokinase (3) adrenocorticotrophic hormone (4) heparin (5) potassium iodide and related to the employment of these drugs neurosurgical measures will also be discussed.

In the third group one has placed the more recent antituberculous agents of the hydrazine derivatives of isonicotinic acid, terramycin, viomycin, neomycin and amithiazone. The discussion on this group will be postponed until the end when future trends of therapy will be reviewed briefly.

Group I - Thiosemicarbazones and Sulphones

Of the three types of drugs mentioned within this group the thiosemicarbazones need be discussed only briefly as they have not been used widely outside Germany where they were employed by Domazek and his associates. These drugs are very toxic and tend to cause nausea, vomiting, drug rashes, haemolytic anaemia, agranulocytosis, albuminuria and liver

damage and therefore for these reasons have not been used as adjuvants in tuberculous meningitis.

The sulphones however have been employed more universally the clinical derivatives of D.D.S. used for therapy being sulphetrone, promin, diasone and promizole, the latter being strongly favoured by Lincoln and her co-workers[28,112,113] in the United States. Looking at table XI again it will be seen that the use of a sulphone has improved the survival rates giving an average of 46.1%. On the other hand we have Madigan et alia (1947)[114], Bunn, P.A. (1950)[48] and Riggins and Gearhart (1949)[115] who all consider the additional use of a sulphone - promizole or sulphetrone - a disadvantage. Bunn comments that on a regime of streptomycin plus sulphetrone there is a poorer survival rate after the sixth month. Guinea-pig[116,117] and rat experiments[118] gave more favourable support to Lincoln's plan of treatment as best results were obtained when streptomycin and a sulphone type of drug was used together, the action of the sulphone being bacteriostatic[119]. Clinical trials of the sulphones in Man were not so encouraging, however, as the animal experiments, promizole appearing the most effective of the four derivatives especially in children. Lincoln and Kirmse (1949)[112] tried the latter drug by itself in tuberculous meningitis without beneficial effect but found it to be of use in miliary tuberculosis.

Promizole is given by the latter workers orally concurrently with intramuscular and intrathecal streptomycin

therapy. Dosage in infants is 0.5 Gm. daily and in older children 1 Gm. daily. This dosage is gradually increased until blood levels of 1 - 3 mgms. per 100 ccs. are obtained within three hours of the oral dose. Therapy, as described by Lincoln and Sifontes (1953)[28], is continued for three years and for at least eighteen months following the last intramuscular injection of streptomycin. Up to 8 Gms. daily in adults has been given. Cocchi and Pasquinucci (1950)[22] also used a sulphone giving it intravenously as they considered that the use of this route reduced the incidence of toxic effects. They used a 60% solution with dosage based on 0.05 - 0.1 Gm. per kilogram body weight per day. A five day rest interval was allowed after each fortnight's therapy. Their results were very good but difficult to assess as other agents were also employed.

Intrathecal sulphetrone was used by Calnan, Rubie and Mohun (1951)[120] as they found that oral and intravenous medication gave poor concentrations in the cerebrospinal fluid. This poor diffusion into the C.S.F. had already been noted in the animal experiments. These authors in two comparable series, one treated with streptomycin alone and the other with the additional use of intrathecal sulphetrone, came to the conclusion that the sulphone was of no advantage the survival rates in each group being similar.

Cathie and Macfarlane (1950)[29] also used sulphetrone intrathecally in addition to streptomycin by combined routes and intrathecal streptokinase and compared cases so treated

with those on streptomycin alone. They formed the impression that sulphetrone, which they considered the least toxic of the sulphone group, did not influence their results for better or worse. They also found that the oral and intramuscular routes did not give high enough cerebrospinal fluid levels of 1.5 mgms. per cent without toxic signs. Their series suffered from the disadvantage of not being strictly comparable.

The balance of evidence does favour improved results from the additional use of a sulphone but usually at the expense of severe toxic effects from the high dosage necessary to obtain satisfactory blood and cerebrospinal fluid levels. These toxic effects, although less severe or dangerous than those of the thiosemicarbazones are a contraindication to their use. These effects may be listed as follows:- haemolytic, iron deficiency and nutritional anaemias, goitrogenic effect, headache, nausea, vomiting, cyanosis, and drug rashes, and result from prolonged administration there being no acute toxic effects of the drug. The sulphones also cause a pink colouration of serum and urine. In animals[121] administration of large dosage of the drug causes in addition a rise in the alkali reserve, a slow absorption from the bowel and a quick excretion by the kidneys. The sulphone passes slowly to the cerebrospinal fluid and doesn't penetrate the brain.

Para-aminosalicylic acid (P.A.S.)

As an alternative to the use of a sulphone which we have seen has certain disadvantages as an adjuvant one may use

para-aminosalicylic acid and table XI,which shows the few series reported, demonstrates a survival rate of 62.9%. Naismith (1952)[52] reports two series of cases, the first treated by streptomycin and the second by dihydrostreptomycin and P.A.S. As has already been stated, dihydrostreptomycin is weight for weight no more effective or rather slightly less effective than streptomycin, so that this author's improved survival rate in the second group might well be due to the P.A.S. However there is the factor that streptomycin and dihydrostreptomycin regimes differed slightly in dosage but this difference is too small to account for the survival rates of 50% in the first and 69% in the second groups. The Council on Pharmacy and Chemistry (1951)[71], Bunn, P.A. (1950)[48], Rossi, Von E. (1950)[122] and Buxton (1951)[123] amongst many others all consider the addition of this drug as an advance in therapy and consider it should be given as a routine. Cocchi and Pasquinucci (1950)[22] used it as well as other adjuvants to therapy. In one's personal series P.A.S. was only administered routinely latterly and given in earlier adult cases only if concurrent pulmonary tuberculous lesions were present, and where a danger of bacterial resistance might develop[124].

Para-aminosalicylic acid can be given orally, by intravenous drip, or intrathecally. The sodium salt is used in aqueous solution and dosage, as employed by Cocchi and Pasquinucci[22] was 0.3 Gm. per kilogram body weight per day divided into three doses. For children they used 0.4 Gm.

Intravenous dose given by drip was 0.5 to 0.75 Gm. per Kilo. body weight per day (in terms of free acid). Intrathecal dose was 50 - 100 mgms. by lumbar route, 50 mgms. by cisternal or ventricular routes and 150 mgms. of a 5% solution subdurally. They considered use of P.A.S. very favourably especially if used when streptomycin resistant organisms appeared and preferred the drug to be given in high dosage by intravenous drip therapy. These authors further stated that P.A.S. was antagonistic to vitamins C and K and therefore gave, concurrently, large doses of the latter. The majority of workers however consider that oral administration is quite satisfactory. It is given as a 20% solution that may cause some nausea and vomiting being very unpleasant to take. It is best administered in small divided dosage three hourly and then this dose is gradually increased to the desired maximum. At first it used to be thought that in the adult 20 Gms. daily were desirable but lesser dosage of 12 - 14 Gms. appears to be equally effective[124,125]. Correspondingly smaller doses are given in children. This drug is best given at the end of a meal as it produces intestinal upset. If the solution is not well tolerated granules or cachets may be used but absorption is not so reliable and if the method of gradual build-up in dosage is employed the incidence of nausea should be small. Treatment with P.A.S. is continued as long as the intramuscular streptomycin is given.

Among the toxic effects of P.A.S. are commonly the above mentioned nausea and vomiting and less frequently pyrexia,

diarrhoea and drug rashes. The use of antihistamine drugs can be invoked as prophylaxis, and desensitisation, if necessary, may be carried out as described by Professor Crofton (1953)[85]. Levels of P.A.S. in the plasma can be potentiated by the use of benemid[69] which delays renal excretion and if hypersensitivity does occur and is resistant to treatment one can fall back on the employment of promizole or sulphetrone.

Para-aminosalicylic acid has been tried alone in treatment of the meningitic and miliary forms of tuberculosis without success[125,126].

Group II - Adjuvants

We have now to discuss the second group of adjuvant agents, members of which have been used in an attempt to overcome the development of adhesions around the base of the brain preventing free circulation of the cerebrospinal fluid and thus of streptomycin (one of the main causes of failure of therapy)[36] and causing hydrocephalus. Post-mortem examination almost invariably has shown the most intense changes, namely greenish-yellow gelatinous exudate and fibrous adhesions, to be in the interpeduncular cistern, the cistern of the lamina terminalis, the cisterna ambiens and extending into the Sylvian fissures. The exudate was more predominant in early cases who had had little or no therapy whereas late cases and those who had had prolonged streptomycin treatment showed the presence of many fibrous adhesions often woody-hard with much fibroblastic activity enclosing active foci of the disease[76]. Associated with these changes there was always some degree of hydrocephalus usually of the communicating type.

A complete block to the cerebrospinal fluid circulation was diagnosed during therapy or at post-mortem in nine patients of this series of 52 cases and in four the hydrocephalus was of the non-communicating type. There was a spinal block in two cases. Furthermore we have also already noted that the meningitis was in certain cases controlled but death had occurred from the reparative late effects of the disease.

Accordingly an agent that could modify or alter this new autopsy picture induced by streptomycin therapy as distinct from that of the more acute type with the gelatinous exudate, would be invaluable, and so within this group we shall discuss such agents.

Tuberculin

Tuberculin used in the treatment of tuberculous meningitis was first described by Don (1907)[128] where a temporary remission in an eventually fatal case was attributed to its intramuscular use. In 1912 Hammon and Wolman[129] in their book described the systemic use of tuberculin in two cases of meningitis with the recovery of one patient. Much more recently Choremis et alia (1950)[61] used in addition to intrathecal and intramuscular streptomycin intravenous injections of tuberculin gradually increasing the strength of the solutions (1 in 10^{-8}) to(1 in 10^{-4}) every four days and continued thus for four weeks. Their survival rate was 61.4%. This form of supplementary therapy has not been used in this manner elsewhere and seemed to be of rather doubtful

efficacy in spite of the satisfactory survival rate. However Smith and Vollum (1950)[26] used tuberculin intrathecally with the idea of destroying the adhesions and the tuberculous granulation tissue in order to allow the streptomycin to reach and attack the enclosed bacillus. Smith (1953)[54] recommends that the tuberculin as a protein purified derivative should be used in minute doses in sensitised patients and she reports two series, one treated with streptomycin and the other with streptomycin and P.P.D. The latter group which all had a graver prognosis showed a better survival rate than the former. Not all cases of tuberculous meningitis have a positive skin sensitivity as shown by the mantoux test, sensitivity being often depressed in this and other fulminating forms of non-meningeal tuberculosis and bearing no relationship to stage of disease[130]. These cases, therefore, not being sensitised to the tuberculo-protein[22,130] would not benefit from the use of intrathecal P.P.D. and, in common with normal patients, no meningeal reaction would occur. Sensitivity can still develop during the course of the meningitis and thus P.P.D. might later be of value. Recommended dosage is less than 0.000,0035 mgm.[50] being related to intensity of the mantoux reaction, and is trebled and quadrupled at four day intervals. Toxic effects can be both dangerous and alarming and include coma, hyperpyrexia, convulsions, raised intracranial tension and acute hydrocephalus with headache and vomiting. As a result of the intense inflammatory reaction of the meninges - a specific tuberculin

reaction (Swithinbank et alia, 1953)[131] - resolution of exudate occurs with high levels in cell count (predominantly polymorphonuclear) and protein rather resembling the spikes following intrathecal streptomycin injection which latter presumably causes release of the breakdown products of the tubercle bacillus. Concurrently with the tuberculin intramuscular and intrathecal streptomycin is given to neutralise the caseous foci thus exposed by tuberculin action (Cairns, 1949)[132]. Post-mortem specimens of brains from cases who have received P.P.D. therapy show remarkably few traces of the basal collar exudate typically found.

In one's own opinion, the severe reactions that accompany P.P.D. therapy militate against its routine use. However this seems to be indicated in those sensitised patients who are not progressing satisfactorily and are beginning to deteriorate with signs of a block in the cerebrospinal fluid circulation and increase in intracranial tension, marked rise in protein levels, steady or falling cell counts and xanthochromia.

Tuberculin given subcutaneously or intramuscularly, although producing a body reaction, does not penetrate the meninges.

As has been detailed two cases in this series received tuberculin treatment, one dying after severe reactions (case No. 18) and the other also with severe reactions benefiting temporarily (Case No. 33).

Streptokinase

Another agent that has been used to remove exudate is streptokinase. This is a bacterial product from haemolytic streptococci (strain 464) which activates a profibrinolysin which in turn lyses fibrinous exudate. It is standardised and concentrated 100 times for intrathecal use and is employed with the object of lysing the fibrino-gelatinous exudate but is of no value against fibrous adhesions and thus it is effective in meningitis in the very early and not the late stages[76]. It seemed a promising substance from in vitro experiments but clinical application has not borne out its early promise. One of its main drawbacks is that it is irritant to the meninges and causes pleocytosis, pyrexia, listlessness, irritability, drowsiness and headache, these symptoms developing in the normal patient and being related, as we have mentioned, to its hydrolysis of plasminogen. Furthermore streptokinase is only miscible with calcium free salts of streptomycin, opalescence also resulting on admixture with dihydrostreptomycin, so that one has to use streptomycin sulphate with it. In the series here analysed seven cases only were treated in part or in toto with the additional use of streptokinase 6 units* being added at each intrathecal injection. No striking benefit seemed to ensue in these cases and rises in cell count and protein level in

* This dose refers to the original B.W.& Co. preparation

the cerebrospinal fluid occurred. This and the other toxic effects made evaluation of the patient's progress more difficult and its further use was discontinued. This impression of streptokinase has been gained also by others and Lorber (1951)[36], Buxton (1951)[123] and Illingworth and Lorber (1951)[38] all write to say that they do not consider it to be of value, Lorber stating that the incidence of blocks in the C.S.F. circulation is not reduced. On the other hand Cathie and Macfarlane (1950)[29] reported favourable results using streptokinase and sulphetrone intrathecally along with streptomycin by combined routes. They found the incidence of blocks less and the survival rate better in a series so treated as compared with one on streptomycin alone. Cathie[35] also believes that streptokinase takes a little time to become effective and reduces the number of intrathecal injections required.

In spite of the latter views, nevertheless, the majority do not advocate the use of streptokinase.

Neurosurgical Methods

In addition to the two adjuvants just discussed neurosurgical methods have been employed to try and overcome the effects of the basal adhesions. As the incidence of blocks to the cerebrospinal fluid may be as high as one in every three cases the decision when and where to use these methods is important and merits discussion next. Their object is usually twofold in that one is to relieve increased intracranial tension and the hydrocephalus and the other to

provide an alternative route for intrathecal therapy. Smith, Vollum and Cairns (1950)[34,50] advise the making of frontal burr holes routinely for ventricular drainage and for therapy, especially if P.P.D. has to be used intrathecally. They state that this method may also help in differential diagnosis as the tubercle bacillus is more often found in ventricular fluid and furthermore histology from pieces of tissue obtained on puncture can be carried out, and the frontal burr holes may be used for ventriculography as an aid in the early diagnosis of C.S.F. block and the assessment of degree of hydrocephalus. If ventricular drainage has to be employed it should be interrupted and not continuous as the latter has been shown to give rise to further blocks through increase in the protein content and in fibrin deposit in the cerebro-spinal fluid[34]. Cairns (1949)[132] stated that drainage of the lateral ventricles continuously was of no value especially in the acute stage and did not lead to lessening of coma, and he tried the direct installation of streptomycin (500 - 1,000 µg. per millilitre (ml.)) through polythene tubes two to four times daily using up to 6 ml. for ten days. The tubes led to the usual site of most intense disease i.e. the interpeduncular region[132] but success was doubtful and there was a danger of pyogenic infection. Should one manage to locate the block to the foramina of Monro, Luschka, Magendie or aqueduct of Sylvius a Torkildsen operation (1947)[133] - a ventriculo-cisternostomy - may be performed but it is rare for these sites alone to be affected[38] as shown by air encephalography.

Major neurosurgical procedures are therefore seldom indicated in tuberculous meningitis, the only one required being the simple provision of a pair of frontal burr holes.

Indications for ventricular drainage are increasing coma or drowsiness, papilloedema or blurred optic disc margins, intractable vomiting, headache, and opisthotonic spasms, the latter three often occurring paroxysmally. Further indications may be increase in pulse rate (a slow rate occurring earlier), Cheynes-Stokes respirations, convulsions, changes in the flow of the lumbar cerebrospinal fluid, and Cocchi and Pasquinucci stress a high protein level with xanthochromia in both lumbar and cisternal fluid specimens. Indications for drainage are usually multiple and often occur early in therapy as demonstrated by pneumo-encephalography (Lorber, 1951)[134]. The Italian authors just mentioned prefer to give ventricular therapy through an indwelling polythene catheter but Cairns and Taylor (1949)[32] have found that therapy by puncture through the frontal burr holes equally easy and effective, the dosage being smaller than that by lumbar route and less likely to produce a reaction by the ventricular route as by the cisternal. Cocchi and Pasquinucci (1950)[22] found that the more extensive use of the cisternal route reduced their mortality and punctures under anaesthesia were not required. As regards spinal block further discussion on the indications and contraindications for the different possible routes of intrathecal therapy in such circumstance will be postponed until management of cases is considered.

The above workers also describe use of subdural therapy and ventricular drainage where tentorial block is present and believe subdural streptomycin can penetrate through the altered arachnoid mater to reach the subarachnoid exudate. They have also tried hydrostatic counter pressure to ventricular drainage for hydrocephalus in order to keep a controlled intracranial tension. They have found that these neurosurgical methods described above, when used in appropriate cases, to have reduced further their mortality rate (Groups III, IV and V - Cocchi and Pasquinucci (1950))[22].

Pontine cisternostomy is described by Komrower (1950)[135] with survival of four out of nine cases. He advocates the use of this procedure if fear of lumbar punctures develops and morale deteriorates, if cerebrospinal fluid rises and/or there is a falling diffusion index (which will be mentioned later) and clinical evidence of an early hydrocephalus. Two other special methods that have been tried but not found to be very successful are the intrathecal injections of air and irrigations with Hartman's solution to prevent adhesions.

It would appear that frontal burr holes should be made in those cases showing signs of deterioration from hydrocephalus in order to carry out ventricular drainage, and in certain cases to help if differential diagnosis is difficult and also to detect the presence and site of a block to the C.S.F. circulation. The burr holes can also be used to supplement lumbar route therapy with intraventricular streptomycin in a non-communicating hydrocephalus, and they can be

used if for any reason lumbar or cisternal routes are impracticable (e.g. The lumbar route was difficult to use in case No. 46 due to Pott's disease of the spine and in case No. 30 due to a pustular rash). This measure is a simple one with danger of infection small and perhaps should have been employed more frequently in selected cases in this series.

Adrenocorticotrophic Hormone (A.C.T.H.)

Recently this hormone has been tried in tuberculous meningitis with the purpose of reducing fibroblastic activity. It had already been used concurrently with streptomycin in the United States for treatment of pulmonary tuberculosis in which thick walled cavities were present. However during this type of therapy some cases have been reported who have developed a complicating meningitis so presumably the converse could happen with a flare-up in the lung lesions. I think one could safely conclude that the use of this hormone would be unwise as it is potentially dangerous and as yet there have been no adequate series reported to support its use. In one recent article[60] in which different forms of therapy were compared, one group received A.C.T.H., isoniazid, intramuscular streptomycin and P.A.S. but it was difficult to evaluate the part played by the A.C.T.H. in view of the different agents employed and the fact that the different series were not strictly comparable as has been pointed out by Lorber (1953)[136]. A.C.T.H. has also been employed in tuberculous meningitis by Halikowski (1953)[137] who presumed that an allergic vasculitis

was causative of decerebrate fits occurring in this disease, the underlying basis being a hypersensitive reaction of the altered blood vessels of the brain. He considered the symptomatology of these "violent neurological reactions" to resemble those in acute disseminated encephalomyelitis in which latter disease A.C.T.H. has been used by Miller (1953)[138,139]. In such cases described Halikowski used increasing doses of the protein purified derivative of tuberculin intrathecally (1 in 10^{-7} solution) every two to three days in doses 0.2, 0.4, 0.6, 0.8 and 1 ml. and then 1 in 10^{-6} solution in the same manner until an inflammatory reaction was produced. He then stopped the P.P.D. and gave A.C.T.H., 15 to 25 mgms. intramuscularly four times daily and claimed a mortality reduction from 68% to 33% with clearing of blocks to the cerebrospinal fluid circulation. During this therapy no other drugs were given. The use of A.C.T.H. to modify the reactions produced by P.P.D. sounds reasonable but dangerous especially without giving streptomycin and one would be very chary of using his technique.

Overdosage of A.C.T.H. will lead to obesity, a moon face, hypertension, oedema, spread of sepsis, and deterioration in tuberculous lesions unless controlled by an antituberculous agent.

Heparin

Heparin has also been tried to reduce fibrin formation and the development of adhesions. Its use was rapidly discarded by those few who tried it as it appeared to be in-

effective and formed a precipitate with the streptomycin salts. It therefore had to be given by separate intrathecal injection about 48 hours after the administration of the antibiotic[86].

Potassium Iodide

One paper[140] also describes the use of potassium iodide in order to try and reduce the formation of fibrous tissue and increase the penetration of the active agents on the analogy of its employment in tertiary syphilis. However there was no evidence of its value as an adjuvant to therapy.

General Non-Specific Therapy

This will include those general measures of a sanatorium type of regime. In this series vitamins A and D, the B complex and C were given orally and if this was not possible by injection until oral therapy could be resumed. The dosage employed was not as large as those of Cocchi and Pasquinucci (1950)[22]. Rectal drips were employed for the first 24 hours following admission in only one or two cases but in the majority with the exception of the moribund dying patient it was possible to give diet by mouth. Blood transfusion or protein hydrolysates by intravenous drip method were not employed although their use has been reported. In the early stage with a restless patient should an intravenous drip be required polythene tubing was employed as this could be threaded some distance up the vein of election and the danger of the tubing being pulled out by the patient's

restlessness was thus minimised. In those patients with also active pulmonary lesions bed rest was prolonged if necessary after cure of the meningitis. Iron medication was also given almost routinely with vitamin therapy.

Depending on the individual patient's progress but on an average about the sixth week of treatment, physiotherapy was instituted provided there was no contraindication such as active pulmonary lesions as just mentioned. Gradually exercises of limbs with preservation of muscle tone was extended so that the patient could sit up. If progress remained satisfactory, the patient was permitted to become ambulant when intrathecal therapy was discontinued and the cerebrospinal fluid was approximately near normal. On an average the patient would be allowed up about the 16th week. Any deformities were splinted under the direction of the orthopaedic surgeon.

Associated with the above was the institution of occupational therapy for the older children and adults. This was found to be quite important from the point of view of morale during such a treatment arduous to doctor and patient alike. Morale was further boosted by the arrangement of cinema shows including cartoons for the young children. One found that morale was not helped by institution of rest periods too early as has already been mentioned.

Ill patients were nursed in cubicle wards and this therefore included all admissions at first and then transferred later with improvement to the general ward.

Sedation by use of barbiturates, was found to be quite satisfactory for use during the day and at night.

Before we discuss finally the third group of the newer drugs and their relation to possible future trends there are a few points in the management of tuberculous meningitis and in the pathogenesis and pathology and complications following therapy worthy of consideration.

The Management of Tuberculous Meningitis

The problems that occur during therapy are those of diagnosis, prognosis, recognition and treatment of blocks to the cerebrospinal fluid circulation (as the management of blocks other than that of the spinal subarachnoid space have been discussed under neurosurgical methods, the latter only will now be stressed),duration of therapy, and detection of relapse or recrudescence.

(a) Diagnosis

All authorities stress the importance of early diagnosis and this is confirmed by the results in table I under analysis of cases. 71% of early cases survived whereas none in the later stage. Therefore consideration of means to facilitate this early diagnosis is important. Careful examination and follow-up of children with a primary tuberculous complex and hilar adenitis in the chest should be carried out as this is the dangerous period for the development of a meningitis before the local lung lesion is controlled[166]. Debré et alia (1947)[141] showed that 42 out of 51 cases who developed an allergy to their primary infection

developed a tuberculous meningitis within six months. Wallgren (1934)[142] has shown that tuberculous meningitis rarely follows careful treatment of a primary infection and states that the dangerous period for development of meningitis usually occurs within four to eight weeks of the appearance of tuberculin sensitivity. But the early diagnosis of a primary infection is very difficult unless an erythema nodosum presents. An uncharacteristic fever in a child merits institution of a period of rest and sanatorium type of regime. This is essentially the prophylaxis of tuberculous meningitis with which, of course, is closely associated the prophylaxis of tuberculous infection anywhere in the body, e.g. vaccination with the Bacille-Calmette-Guérin (B.C.G.), clean milk supplies (case 25 died from meningitis through a bovine organism obtained in drinking raw milk), proper isolation of known cases and follow-up of contacts. An example where prophylactic measures in childhood tuberculosis including meningitis have borne fruit is in Sheffield where childhood mortality figures have improved markedly. These measures included thorough contact examination, segregation, B.C.G. vaccination, streptomycin therapy, and the establishment of a follow-up clinic for small children including those suffering from a primary lung infection (Lorber, 1953)[143].

Wallgren further proved the relationship of the primary infection to tuberculous meningitis by showing graphs with corresponding peaks of incidence in either

condition there being a time lag of six to eight weeks later in the meningitis. These curves also showed that the peak incidence was in the late or early spring for the primary infection and the tuberculous meningitis, occurring six to eight weeks later, had its peaks in late spring or early summer[144,145]. Prophylactic therapy in Gothenberg, Sweden[142] over six years reduced the total incidence of tuberculous meningitis and therefore, although potent anti-tuberculous agents are now available, prophylaxis must not be overlooked as a therapeutic weapon. In this series 19.2% of cases had evidence of an active primary chest infection.

Occasionally diagnostic lumbar puncture should be considered during a primary infection if additional symptoms and signs of headache, vomiting and mental change develop even without those of meningeal irritation. An early lumbar puncture may thus reveal a simple serous tuberculous meningitis with its better prognosis and easier treatment than the later sequel of a frank meningitis[46].

Further precautions to aid detection of tuberculous meningitis early are those of routine lumbar punctures at commencement of and weekly or fortnightly during treatment of a miliary tuberculosis[38,146]. Case 30 is an example where this should have been carried out as earlier recognition of the meningitis would have been achieved. Often, however there are no physical signs or symptoms to suggest the onset of this complication during the course of the miliary disease. It has been pointed out above that two cases in this series

developed tuberculous meningitis after completion of therapy and cure of their miliary tuberculosis, and indeed cases have been reported where this has occurred as late as the seventh month following treatment[49]. Therefore it would seem wise to continue with a few diagnostic lumbar punctures during the follow-up period of such patients.

Apart from alertness during a primary infection, during miliary disease, and even during tuberculous osteomyelitis of the spine, the analysis suggests that headache, vomiting, constipation, pyrexia and loss of appetite that persist and are accompanied by a change in the patient's normal personality towards lethargy or apathy[27], with moments of irritability, are warning early manifestations and therefore one should not await neck stiffness or a positive Kernig's sign or other neurological signs which develop at the end of the prodromal stage or even later. Thus, to achieve early diagnosis, the above group of symptoms with emphasis on mental change[144], should be treated with great respect especially if accompanied by a positive family history of tuberculous disease or a tuberculous infection of one type or another (e.g. tuberculous hip disease in case No. 10; pleural effusion in case No. 17). Early diagnosis facilitates institution of therapy before the exudate organises into the fibrous adhesions which cause so many of the troublesome late effects.

Differential Diagnosis

Passing from the problem of early diagnosis the next

difficulty encountered is often that of differential diagnosis. Many points in regard to the latter have already been mentioned in the analysis and one will try to avoid repetition. In many cases the diagnosis is not difficult but atypical cases occur and the list of conditions that may have to be considered in the patient presenting with unusual features is given in the analysis. Here it is that careful routine examination on admission pays dividends and therefore present, past and family history, the mantoux reaction, the physical examination, examination of eyes and cerebrospinal fluid and chest X-ray all play their part.

(i) Clinical History - The history of the present illness may not be helpful and is often vague. It may be short or long and unrelated to the stage of the disease but the exposure to risk of the intake of raw milk in a child, a previous precipitating illness such as an infectious fever or trauma (occurred as a doubtful cause in 2 cases) which may light up a perifocal reaction around an established intracranial focus[27,113,145,147](four cases in this series), the story of a recent or past tuberculous infection elsewhere in the body (the primary site may be thoracic, abdominal, cervical or bony[145], or even a tuberculous otitis media (Crowe,1930)[148]) may be the factor which helps to tip the scales in favour of a firm diagnosis. Of greater help in differential diagnosis is a history of possible contact with a tuberculous person, usually a member of the family circle although actual contact may be difficult to prove.

Lorber (1950)[149] found the source of infection in 80% of 123 adequately investigated cases of miliary and/or meningeal tuberculosis and noted that mismanagement in supervision of tuberculous adults was a serious factor capable of correction. Wilson et alia (1952)[150] quote contact figures of 39.5% for England, 22.8% for Wales, and 28.9% for Scotland. Lincoln (1947)[166] found a contact history in 58% of children with meningitis and the Medical Research Council (1948)[25] quoted 38%. I think that in this present series the figure of 29% of cases with a positive contact history could have been improved by more diligent search.

(ii) Mantoux test - The mantoux test was found to be a valuable aid in diagnosis in differential diagnosis in the very young as it is usually positive in tuberculous meningitis but Taylor, Smith and Vollum (1953)[130] warn that skin sensitivity on admission can be low or absent irrespective of stage of the disease. The performance of serial mantoux tests are then indicated as sensitivity may develop later. Choremis (1950)[61] considers that streptomycin reduces tuberculin sensitivity.

(iii) Examination of the eye - A further important step towards diagnosis is careful examination of the eye and, as has been mentioned in the analysis, the discovery of choroidal tubercles is important. These are present in miliary tuberculosis with meningitis more frequently than without the latter, and the overall incidence quoted in the exhaustive survey by Illingworth and Wright (1948)[30] was shown to be 28%

of cases. Tubercles are rarely found in meningitis alone or in the other forms of tuberculosis and the change in their appearance during therapy is an aid in prognosis as will be stressed below. In this series 3 out of 10 patients with miliary disease and meningitis or three out of the total 52 cases were found to have choroidal tubercles. Debré et alia (1947)[141] found a very much higher incidence of 75%; Lincoln (1947)[166] found an overall incidence including cases of tuberculous meningitis of 10%; Lorber and Emery (1950)[31] reported an overall incidence of 52% of children with miliary lung tuberculosis had tubercles; and Bernard et alia (1947)[43] found 25% of cases with miliary and/or meningeal tuberculosis, and if the miliary alone were considered 34% were so affected. Dr. Monbrun (Paris)[73] gave the highest percentage of 87% of cases with miliary and meningeal tuberculosis or 17% for the meningitis cases only. Thus the incidence in this series seems to be too small and could have perhaps been increased if the sedation technique as described by Illingworth and Wright had been employed.

Various other eye changes that may be present are papilloedema, optic atrophy, retrobulbar neuritis and disturbances in the intrinsic and extrinsic motility of the eye. Ocular symptoms and signs in meningitis treated by streptomycin are well described by Mollaret (1949)[151] who puts a high incidence to choroidal changes. Examination of the eye may, therefore, be of great diagnostic help.

(iv) Radiology - Radiology by revealing the presence of tuberculosis elsewhere, usually, in the lungs, is a further valuable aid and, as the analysis shows, 33 out of 46 cases X-rayed had pulmonary lesions, the commonest being the primary infection and miliary disease. An interesting point is the number of adult cases whose pulmonary lesions improved during therapy for the meningitis only to relapse later or on the contrary for pulmonary lesions to become apparent after cure of the meningitis e.g. case No. 6 where enlargement of paratracheal glands appeared; case No. 11 where deterioration took place, and case No. 41 whose pulmonary condition relapsed later under the strain of a pregnancy. Special consideration of therapy for both pulmonary lesions and the meningitis is necessary with prolonged sanatorium treatment, and delay in allowing too early physical activity and ambulation. Use of adjuvants to delay or prevent the development of bacterial resistance is especially important in such cases as much as their use for synergistic action and one should not hesistate to use radical surgical methods to eradicate any lung focus of activity if surgery is indicated once the meningitis is controlled. Case No. 11 who eventually died from pulmonary phthisis had a meningeal infection which was controlled moderately rapidly and it is conceivable that surgery carried out earlier in his case might have saved his life. He also did not receive para-aminosalicylic acid which was just becoming available at this time, and later developed a streptomycin resistant organism for which thiosemicarbazone was tried with-

out improvement. Thus this eradication as soon as practicable e.g. after sixth week of intrathecal therapy of a pulmonary focus which may be active and could give rise to further metastatic spread appears logical. The presence of adult phthisis and to a much greater extent miliary disease makes the prognosis more serious and Smith, Stevens and Pile (1951)[152] stress these dangers of pulmonary tuberculosis complicating a meningitis.

Some examples of the X-ray films of patients in this series are included in the Appendix, those of cases Nos. 6 and 47 being especially interesting.

(v) Examination of the cerebrospinal fluid - This is the most helpful of all the different methods in differential diagnosis. A rise in protein levels, a lymphocytic increase in the cell count, a low chloride and a low sugar value, are the most important diagnostic points, the latter being the most useful. However it has been shown in the analysis that border line cases occur in which the sugar and chloride level may even be normal and Lincoln (1947)[166] describes three such instances. Chloride levels however are not reliable as they are lowered by dehydration and vomiting. In the doubtful case the Levinson test and colloidal gold range could be of limited help as they are normal if there is no meningeal inflammation. Repeat lumbar puncture after a few days may help by giving a more typical picture and, if in the meantime intramuscular streptomycin is given and cerebrospinal fluid levels show a rise to 0.5 µg. per ml. or more it would suggest a meningeal

inflammation. Failing bacteriological confirmation by film one must not delay too long for result of culture or guinea-pig inoculation and should proceed with therapy on a presumptive diagnosis although realising that one is subjecting the patient to a prolonged severe form of treatment. Subsequent behaviour of the cerebrospinal fluid as regards protein and cells may show the fluctuations which are pathognomonic of tuberculous meningitis[50] and which do not occur with streptomycin given intrathecally in normal cerebrospinal fluid or in other meningitides such as haemophilus influenzal meningitis.

Differential diagnosis is made easy, however, if tubercle bacilli are actually seen in direct film made from the cerebrospinal fluid. A spider web clot in the fluid is significant and a film from the 'spun' sediment of the latter often reveals the presence of bacilli. Large samples of fluid for examination increase the chances of obtaining a positive result[49] but one must exert care in withdrawal if there is much increase in intracranial tension. Samples by cisternal[22,145] or to a less extent intraventricular puncture also increase the chance of a positive result. In this series the presence of tubercle bacilli was seen in only five cases and this seems inadequate as other authors report a much larger number of positive results, e.g. Rubie and Mohun (1949) 58%[27]; Cathie and Macfarlane (1950)[29] 88% using a technique whereby pinhead drops of sediment after centrifuging the cerebrospinal fluid were examined instead of by smear;

Choremis, K.(1950)[61] 37.8%; Cocchi and Pasquinucci (1950)[22] 91% by direct microscopy, the latter authors declaring that this is more reliable than cultural methods; and the Medical Research Council (1948)[25] 46%. However it is only rarely in tuberculous meningitis that the presence of tubercle bacilli is not confirmed by cultural and/or animal inoculation methods provided samples are examined on repeated occasions early in therapy. The percentage of positive results obtained by these further measures is close to 100% in all the series quoted above. In certain selected cases where there is difficulty, culture and animal inoculation of specimens of urine, sputa, gastric washings or laryngeal swab should not be forgotten as means of obtaining the causative organism. Occasionally the culture will be positive and the animal inoculation negative and vice versa. A survey of this series would suggest that the guinea-pig inoculation is slightly more reliable than culture, 37 to 32 positives respectively, and would agree with the findings of the Medical Research Council (1948)[25] and of Macgregor and Green (1937)[153]. Blacklock and Griffin (1935)[145] however state that the cultural method is quicker and more reliable for the human strain whereas the guinea-pig test is better for the bovine strain. The answer is, of course, that one must employ both methods.

The incidence of the bovine strain was 12.5%, i.e. four cases out of 32 positive cultures. This figure seems slightly less than most published series taking into account that the patients were drawn from a semirural community.

The Medical Research Council series (1948)[25] states that 1 in 33 cases was of bovine strain but Blacklock and Griffin (1934)[145] gave a higher figure of 22.5% and Griffith (1934)[154] quoted an overall percentage of 25.5 - England 151 cases with 33 (21.8%) of bovine strain and Scotland 37 cases with 15 (40.5%). Recent figures given by Wilson and his associates (1952)[150] in their handbook 'Non pulmonary Tuberculosis of Bovine Origin in Great Britain and Northern Ireland' were as follows:-

England 1943-45	28%	Overall 16.4%
Wales 1943-45	10.1%	
Scotland 1943-45	11.1%	
Nth. Ireland 1945-50	3.4%	

Munro and Scott (1936)[155] published a series in which 36% of cases of meningeal tuberculosis were due to the bovine bacillus (21.9% urban and 60.1% rural) and McDougall (1949)[156] quotes 24.6% for England and 28.6% for Scotland which seem rather high figures. Most countries other than Denmark and Britain report a low incidence of bovine tubercle bacilli causing meningitis.

(v) Simple serous tuberculous meningitis - Positive bacteriology will therefore clinch the diagnosis but before one leaves this subject mention should be made of simple serous tuberculous meningitis. Two cases in this series were presumed to fall into this category (cases Nos. 45 and 47). They both had known active tuberculous lesions in the chest under treatment and both developed headache, pyrexia and vomiting.

There were no signs of meningeal irritation but lumbar puncture in each case revealed a cerebrospinal fluid with normal chemistry and sugar levels but with an increased cell count predominantly lymphocytic. No positive films, cultures or animal inoculations were obtained in either instance and both resembled cases as described by Lincoln (1947)[33] as serous tuberculous meningitis. She explains the mechanism as a perifocal reaction around an older tuberculous cortical focus or as a cortical seeding during a flare-up in a concurrent chest lesion. This mechanism would probably explain many of those cases of tuberculous meningitis which have in the past been reported as spontaneous cures[1-4]. Occasionally tubercle bacilli are isolated from the C.S.F. of such cases[4,71,157-159] and they represent a potential danger as they may cause a tuberculous meningitis later this having been confirmed by follow-up. Post-mortem examination has shown in some who had subsequently died caseous foci in the cortex without a meningitis but sometimes there was evidence of a non-specific meningeal reaction[33]. This serous meningitis with a normal chemistry of the cerebrospinal fluid is most liable to occur during a primary infection, during a flare-up of a tuberculous lesion, during an infectious fever, after tuberculin testing, or even after exposure to strong sunlight[166]. Lincoln and Sifontes (1953)[28] and Choremis, K. (1950)[160] do not advise therapy unless there is miliary disease present (former authors) but personally one should agree with Cairns, Smith and Vollum (1950)[50] in

carrying out treatment for six weeks or longer. In case No. 45 it might be argued that the cerebrospinal fluid change was due to an encephalitis following the chickenpox but I considered the change to result from a perifocal reaction as described above activated by the varicella and the subsequent behaviour of the cerebrospinal fluid would suggest the presence of a meningitis rather than an encephalitis (see Appendix). Therapy with streptomycin by combined routes is the safer and wiser course and may well prevent the fully developed disease occurring later.

Cohen and Wood (1938)[161] describe cases of exudative pulmonary tuberculosis in which headache and vomiting develop but the cerebrospinal fluid is quite normal except for increase in pressure. These cases resolved spontaneously (as do the simple serous type) as far as the symptoms were concerned and the authors believed there to be an allergic exudation into the meninges of clear fluid. They called these cases cerebral paratuberculosis and distinguished them from the serous meningitis.

Differential diagnosis may be further helped by ventriculography as has been mentioned under neurosurgical methods.

(b) Prognosis

The art of prognosis in respect of life and quality of survival is a difficult one especially in a disease of such long duration as tuberculous meningitis where a patient may progress well or relapse even as much as 12 - 18 months

later. Reference to the analysis of cases presented above and to other series shows that a favourable factor is early diagnosis which has already been stressed, this diagnosis leading to commencement of therapy with the disease in the early stage. However one may have a case with the meningitis of short duration and concurrent advanced pulmonary or miliary lung disease and therefore advanced non-meningeal tuberculous lesions militate strongly against a favourable outcome. An active primary infection and specimens of cerebrospinal fluid giving repeated positive cultures and/or guinea-pig inoculations in spite of therapy all add up to a worse prognosis[24]. In this series and many others the presence of miliary disease[55,162] and choroidal tubercles carried a higher mortality and therefore these complications demand more prolonged treatment than usual. Illingworth and Lorber (1951)[38] had survival rates with this combined infection equalling those of meningitis alone but this experience is exceptional. The age of less than three years is also an adverse factor[24] as far as prognosis goes and this has been pointed out in the analysis above with the reasons that are probably the cause. Here again Illingworth and Lorber (1951)[38] found the survival rates in the groups under and over three years to be similar but again this is contrary to the general run of experience. Favourable signs during therapy are early improvement in the mental state, gain in weight and in general physical well-being usually occurring after the first six weeks of treatment. A rise in the cerebrospinal fluid sugar levels is a very good sign, and this is further

reinforced by a falling cell count, and of less importance a falling protein level and a rise in the chlorides. If streptomycin assays are carried out on the cerebrospinal fluid and show a fall in content this indicates less meningeal inflammation and so a favourable trend. Choremis et alia (1950)[61] uses the alkaline phosphatase levels in the cerebrospinal fluid as a measure of progress and thus an aid to prognosis. The phosphatase is uninfluenced in vivo or in vitro by streptomycin, parallels inorganic phosphate levels and can be measured in Bodansky units (U.B.) as follows:-

Normal	average 1.4 - 1.6 U.B.	Applicable to ages 4 - 14 yrs.
Advanced disease	average 0.4 - 0.8 U.B.	
Improved	average 0.8 - 1.1 U.B.	
Clinical restoration	average 1.0 - 1.4 U.B.	

and this appears as if it may be of some value in special cases. Choremis in another article (1948)[146] mentions also that the cerebrospinal lipase is low in advanced disease and rises as recovery occurs.

Resolution of papilloedema and other ocular symptoms[61,152], and paling of choroidal tubercles, with pigmentation around their edges and an eventual white parchment-like central appearance are all favourable prognostic points. The corollary of the appearance of fresh tubercles and failure of those already present to heal are bad signs. These changes in tubercles are detailed further by Illingworth and Wright

(1948)[30], by Mollaret et alia (1949)[152] and by Sommer (1950)[75], and complete healing usually takes about eight to twelve weeks, the choroid around them finally paling also.

Improvement in the radiological picture may also be a good sign but some caution here must be exercised as post-mortem examination has confirmed clinical assessment in that the pulmonary lesions have healed and the meningeal may be active[25,55]. The reverse also occurs and often the miliary disease is first revealed at autopsy.

Complications developing during therapy adversely affect the outcome as might be expected. These complications are mainly those resulting from fibrous adhesions and exudate in the interpeduncular region where the disease is commonly most intense. As a result hydrocephalus and blocks (including spinal) to the C.S.F. circulation and brain softening from infarcts due to a tuberculous endarteritis occur, and although the inflammatory process may be quiescent these complications kill or leave a patient paralysed, hemiplegic and rarely mentally defective. Amongst other resultant complications described, there are blindness, bulimia, logorrhoea, arterial hypertension, glycosuria, sleep disorders, these latter usually resulting from a hypothalamic or pituitary upset[34], behaviour upsets (case No. 34), terror starts (case No. 50) and a Korsakow's psychosis. Too intense intrathecal therapy appears to leave a poorer quality of survivor.

The presence of neurological complications on admission with coma or marked mental upset, a negative mantoux reaction[22,130],

and bacterial resistance, rare in tuberculous meningitis[25,38,110], all indicate a bad prognosis whilst decerebrate rigidity with intense basal exudate and a tuberculous arteritis with infarcts of the basal ganglia give a virtually hopeless outlook. At the other extreme there is the serous type of meningitis with a very good prognosis.

Thus to prognosticate the whole clinical picture over a few weeks requires to be assessed and this is helped by using special charts[32] and graphs of the type shown in the Appendix, in which charts, progress in weight, resolution of pyrexia and cerebrospinal fluid trends can be seen at a glance. In management of this disease regular complete checks of the patient by physical examination, X-rays, ophthalmoscopy and diagnostic lumbar puncture are required. Very often when a block occurs, with its more unfavourable prognosis, one must remember that it may resolve spontaneously[55] (case No. 17) with or without a rest from intrathecal therapy and then again the rest may often lead to improved well-being and weight gain. Prognosis therefore, although guarded, need not always be unduly pessimistic. Another point, although not quite so obvious, is that these cases should be treated in centres with the special experience in their nursing and medical care, and with good laboratory and specialist services. If relapse or recrudescence does occur response to further therapy is usually more favourable[61]. One should also consider in assessing prognosis the innate resistance of the individual to the tubercle bacillus and the

latter's virulence, e.g. this resistance is lower in the jewish and negroid races[147].

(c) Recognition and Therapy in Spinal Subarachnoid Block

Another important point in therapy is the early recognition of a spinal block. Other blocks to the cerebrospinal fluid with their signs and symptoms and treatment have already been mentioned under neurosurgical methods page 98. A block in the spinal subarachnoid space is shown by a rise in the protein content, xanthochromia and a fall in the cell count of the lumbar cerebrospinal fluid with often a scanty flow of the latter. Radiculitic pains shooting down the lower limbs, backache and girdle pains, and pain during lumbar injection are also warning symptoms. The Queckenstedt test showing a failure to rise or a slow rise without fall in the C.S.F. pressure on jugular compression indicates a complete or a partial block respectively, and the estimation of the diffusion index as described by Comparetti et alia (1948)[163] may help in the early recognition of this complication. This diffusion index is defined as the ratio of the concentration of streptomycin in cerebrospinal fluid obtained on cisternal puncture to that in the lumbar fluid eight hours after the injection of 30 mgms. of streptomycin. When the index is low, intrathecal injections should be given by cisternal or ventricular routes. These authors suggest that the index should be estimated regularly every two or three weeks during therapy and the use of this index is further described in relation to a series of cases by Cocchi and

Pasquinucci (1950)[22]. These authors state that it is more sensitive and reliable than the protein levels in cisternal and lumbar fluids, low and high readings respectively suggesting a block. Lorber (1950)[164] also found the lumbar/cisternal protein ratio was unreliable. Few indications (usually temporary) present for total abandonment of lumbar route for intrathecal therapy. As has been mentioned, when blocks occur with a non-communicating hydrocephalus therapy by ventricular route to supplement the lumbar route is often of value. Frequently by using the alternative route and resting the lumbar one the spinal block may clear spontaneously even after four months of daily cisternal punctures - Flori (1950)[165]. Skin rashes and vertebral disease may also lead to temporary abandonment of the lumbar route.

Therefore, should a spinal block develop one would suggest cisternal punctures on alternate days and weekly lumbar punctures, therapy being given by the cisternal route. Should there be no signs of rapid clearing of the block within two weeks, therapy should be continued by the ventricular route as being of less danger and inconvenience than the cisternal[32], until the spinal block resolves (if at all). The dosage by cisternal or ventricular route should be slightly less than that by lumbar.

(d) Duration of Therapy

The decision when to discontinue intrathecal therapy is a difficult one more so than deciding when to stop all

treatment including that during the follow-up period after discharge from hospital. Criteria that aid in this decision regarding intrathecal therapy are the return of the sugar levels in the cerebrospinal fluid to normal levels and of lesser importance return of chlorides to their physiological values. Return of cell count and protein level to approximate normality (for normal values see analysis) will also favour cessation of treatment. Other favourable indications are negative bacteriology as regards films, cultures and guinea-pig inoculations, the results of the latter two being referred to specimens withdrawn six to eight weeks earlier. The patient's improvement in general condition, physical and mental state, continued rise in weight, a normal temperature, improvement and clearing in chest complications elsewhere, and healed choroidal tubercles are all further favourable signs that therapy may be discontinued or gradually tailed off. A normal Lange gold curve or Levinson test[22,112], and an alkaline phosphatase returned to normal are absolute criteria of the return of the cerebrospinal fluid to normality but these tests are perhaps too exacting as they often follow after some months of clinical cure. Choremis et alia (1950)[61] states that lessened skin sensitivity to mantoux tests and an erythrocyte sedimentation rate that has returned to normal precede the normal C.S.F. Other authorities disagree regarding the skin sensitivity and believe that it rises to a maximum during the disease and remains at that level.

This decision to stop intrathecal treatment should

be made on an assessment of several specimens of the cerebrospinal fluid and on the patient's general progress during two to three weeks. One would advise, if all is satisfactory, that the intrathecal course should not be stopped immediately but should be gradually tailed off with the intermission of frequent rest periods during which a careful watch is made for progress or deterioration. The details of this lessening in intensity of therapy and of procedure in follow-up has already been detailed under the analysis of cases.

More prolonged therapy for a further two or three weeks should be given for cases with extensive pulmonary lesions of adult phthisis or miliary type. Each case has to be judged on its merits and no hard or fast rule employed.

On an average it is about the twelfth week of combined treatment when one begins to consider seriously when intrathecal treatment can be decreased. If the patient's satisfactory progress is maintained on the less intense therapy, this latter may then be discontinued but follow-up diagnostic lumbar punctures should still be performed at gradually increasing intervals of time.

During the whole course of the disease and less frequently in the follow-up period complete assessments as have already been detailed should be carried out and in between these, a less complete examination with daily check on progress of cells and protein in C.S.F. should suffice unless complications indicate otherwise. The check on cells and

protein will then help to warn against the development especially of a spinal block.

In this series the graphs of the behaviour of the C.S.F. elements during therapy will show that sugar and chloride estimations should have been carried out more frequently but it was not until later that the value of the sugar level especially was appreciated.

During the follow-up period the intramuscular streptomycin is given for two to three months after cessation of intrathecal treatment and para-aminosalicylic acid should be continued, concurrently.

(e) Recognition of Relapse or Recrudescence

As has already been stated, prognosis in tuberculous meningitis has to be guarded in view of the danger of relapse or recrudescence which terms have already been defined. The danger of relapse recedes after the first twelve months from onset of therapy but when it does occur it is usually heralded in by symptoms and signs which often precede changes in the cerebrospinal fluid. A fall or failure to rise in weight, return of headaches, often accompanied by vomiting, personality change, irritability and lethargy, and pyrexia are the warning manifestations and it is only later that there may be a return of the signs of meningeal irritation, i.e. neck stiffness and positive Kernig and Brudzinski signs. Choremis et alia (1950)[61] state that return of papilloedema after cessation of therapy is one of the earliest signs of a relapse and Cocchi and Pasquinucci (1950)[22] say that change

in a Lange colloidal gold curve in the C.S.F. that has been normal is also one of the earliest warning signs.

Of the changes in the cerebrospinal fluid that accompany or follow the clinical signs, a low sugar content even if the other elements be normal and positive bacteriology obtained by any of the routine methods that had yielded negative results previously, will indicate that a relapse of the disease has occurred or is imminent. The mechanism of this relapse is very often related to foci of infection which are locked up by adhesions, the cerebrospinal fluid having become normal after 12 - 16 weeks treatment, and then with a breakdown of one of these sites of activity the disease starts afresh[24]. Very soon after the prodromal symptoms and signs, the C.S.F. will once again show the characteristic picture.

Recrudescence of the disease occurs whenever therapy becomes less intense or is discontinued and is manifested by rising or fluctuating cell counts, falling sugar levels and rise in streptomycin content in the cerebrospinal fluid. Deterioration in general condition, stationary or falling weight curve, and rise in pyrexia also occur as in relapse.

The main problems that occur during the management of a case of tuberculous meningitis have now been discussed, along with their relationship to treatment, but before we consider finally future trends in therapy there are two subjects worthy of consideration, namely, the complications that may follow therapy and pathogenesis and pathology.

Complications following Therapy

The analysis will show that the quality of survivors in this series was good, the main complications being deafness or vertigo or both due to streptomycin. The only case with marked physical defect was No. 6 (see Appendix) and two cases (Nos. 34 and 51) had behaviour disorders from which recovery was made. Indeed an impression was gained that in several of the children (detailed in the analysis) their mental state regarding intelligence was better after the disease than before its onset. Cocchi and Pasquinucci (1950)[22] also remark on this stating that mental and physical state in some of their survivors was better than for many years prior to their illness.

Small intrathecal dosage given over a prolonged period may be a factor in the satisfactory state of the survivors but the main reason for the low incidence of complications was undoubtedly that it was only the early cases that survived.

Complications following therapy and resulting from the disease process that have been described in the literature are blindness, optic atrophy, cerebral thrombosis, hemiplegia usually of facio-brachial type, spastic paraplegia, mental deterioration, Korsakow's syndrome, decerebrate rigidity and the hypothalamic disorders that have already been mentioned. Two rarer and interesting complications were described by Lorber, the first being ectopic calcification occurring in a case of tuberculous meningitis

with a spinal block and paraplegia in flexion[167]. The metastatic foci of ossification appeared about two to six months after the onset of the paraplegia and most were found in the adductors of the thighs. Operative treatment to remove these foci aggravated a very disabling condition.

The second unusual complication following therapy which he described, was sexual precocity in a case with the menarché at 7½ years[168]. A marked hydrocephalus, calcified intracranial tuberculomata, cerebral cyst and optic atrophy with good vision were present and presumably this precocity was secondary to hypothalamic or pituitary damage occasioned by the hydrocephalus.

This damage is, no doubt, also related to the obesity syndrome that occurs in children recovering from tuberculous meningitis as described by Choremis et alia (1950)[61] and Lorber (1951)[168]. Similar hypothalamic manifestations to those just mentioned above and to others stated earlier have been found to develop in cases with tumours in the region of the third ventricle.

Russell and MacArthur (1953)[56] in a 4 year follow-up of their cases of treated tuberculous meningitis noted intracranial calcification in ten out of thirteen patients surviving long enough for it to occur. This is not perhaps a complication and might be a useful index of healing but Cairns (1951)[169] warns that the exudate in tuberculous meningitis may persist for many months or indefinitely and become calcified and therefore calcification is not an in-

fallible sign of healing. He quotes two cases with calcification who relapsed and died.

Most of these complications which have just been described result from the hydrocephalus, the tuberculous endarteritis and the fibrous adhesions and exudate that occur in streptomycin treated chronic tuberculous meningitis.

Pathogenesis and Pathology

To understand some of the principles of treatment of this disease and its complications it is necessary to mention briefly pathogenesis and pathology, and that is why no apology is made for introducing this subject to a discussion on aspects of therapy.

Originally it was believed that tuberculous meningitis resulted from haematogenous spread usually of a miliary infection leading direct to the meningitis. However Rich and McCordock (1929)[170] and (1933)[171] produced very convincing experimental and morphological evidence that diffuse tuberculous meningitis resulted from discharge of bacilli into the cerebrospinal fluid from adjacent older caseous foci such as cortical tuberculomata or caseous bony disease. They found such foci after careful search in the brain, the spinal cord, the meninges, the choroid plexus and in the bones encasing the nervous system in 77 out of 82 cases. Some of the experimental evidence they produced in support included their failure to produce tuberculous meningitis by introduction of virulent tubercle bacilli into the bloodstream, their success when the bacilli were introduced into

the cerebrospinal fluid, the fact that the meninges had very little tendency to arrest inert circulating particles, and the fact that at autopsy the age of the visceral tubercles did not correspond with that of the meningitis, one being early and the other late or vice versa. They also demonstrated by the use of carbon particles that tubercle bacilli can spread retrograde to the flow of the cerebrospinal fluid and thus cause tubercles of the ependyma or choroid plexus, indeed more frequently than from the bloodstream. They also believed that the vascular alterations were due to the tuberculous exudate in which the vessels lay, and were not due to haematogenous spread[172,173]. Histological examination confirmed this showing most marked changes in those vessels lying in thick exudate. These changes were mononuclear infiltration and fibrinoid necrosis of the adventitia with proliferation of the intima and narrowing of the lumen[173-175]. The meningeal veins might also be intensely involved, just as the arteries, and Schwarz (1948)[176] believes that a final miliary spread can occur as a result of haematogenous dissemination from the phlebitis as well as from cerebral or meningeal tuberculomata.

The theory that these cortical foci seed during a previous bacillaemia such as might occur in a primary infection fits in well with all the known facts and would explain the mechanism of the simple serous meningitis as already suggested, i.e. a perifocal reaction around a meningeal or cortical tuberculoma during which reaction and before the

new seeding has been walled off by the body's defence mechanisms, a few bacilli may escape into the cerebrospinal fluid. Support to the Rich theory is also given by Macgregor and Green (1937)[153] and Walker (1935)[177] from evidence of their autopsy examinations and it is now generally accepted although in 1936 Ragins[178] studied 47 patients and stated that in only seven could he find evidence that an older tuberculous focus had caused a diffuse meningitis.

Amongst the changes found at post-mortem[179] many of which have already been mentioned, are a greenish-yellow fibro-gelatinous exudate which is thickest in the inter-peduncular and associated cisterns. There is lateral extension into the Sylvian fissures and the midbrain is encircled. The arteries in association with the circle of Willis are deeply involved with an endarteritis and narrowing of their lumen[173]. Streptomycin therapy aids healing which occurs by dissolution of fibrin with replacement by actively proliferating fibroblasts infiltrating or encapsulating foci of necrosis. The proliferative endarterial reaction is accelerated by the streptomycin and the stenosis or occlusion of the vessels leads to cerebral anoxia and worse still, infarction often of the basal ganglia with shrinkage of brain tissue. It is this latter that leads to most of the irreversible neurological sequelae and the hypothalamic or pituitary syndromes.

The intense basal exudate will itself lead to tentorial block to the cerebrospinal fluid circulation with a communicating hydrocephalus and eventually this exudate as it resolves may become woody hard or calcified. Thus the outstanding complications pathologically of a streptomycin treated case are a communicating hydrocephalus and multiple ischaemic brain softenings. In most cases the posterior portion of the basal cisterns are clear[25] but Smith, Vollum and Cairns (1948)[34], and Cairns (1949)[132] state that gravity acts unfavourably on the meningitis and exudate gravitates to the posterior horn of the lateral ventricles, and is more intense on the dorsal than on the ventral surface of the cord from result of the dorsal decubitus. One such case is specifically quoted by these authors and they suggest that if possible the patient's position should be changed now and then, and they observe, in support of their theory, that a restless patient often does better than a quiet one.

Two further features described in the literature are those of a tuberculous encephalitis and ependymitis. The encephalitis[25] is often found localised in the sulci of the cerebral and cerebellar hemispheres; the ependymitis[127] proceeding to formation of subependymal tubercles and later gliosis has been described as leading to persistent granularity of the ependyma.

This latter and the majority of the other appearances which have just been mentioned were found at post-mortem in

in this series of cases and for further detail the case records in the Appendix may be consulted.

One can, therefore, deduce that if these vascular changes and the hydrocephalus are marked a successful result, whatever form of therapy is employed, is virtually impossible.

Causes of failure in treatment could, thus, be listed as (1) severe hydrocephalus of communicating or non-communicating type (2) severe arteritis and cerebral infarction (3) widespread meningitis (4) therapy commenced too late (5) therapy stopped too soon (6) extensive active or miliary tuberculosis elsewhere (7) rarely development of bacterial resistance.

Group III - Isoniazid

Finally, by way of conclusion, there remains the discussion of the third group of adjuvants or antituberculous agents with their possible bearing on future trends of therapy - an interesting speculation in view of their promising features. This applies especially to the most important, namely, isoniazid, or isonicotinic acid hydrazide which was first discovered by American workers in 1951 and found to have a marked tuberculostatic activity even greater than streptomycin[180]. At the same time as the latter was under trial isonicotynal hydrazine which, with isoniazid forms one of two closely related derivatives of isonicotinic acid, was tested but found to be the more toxic[181]. However the toxic effects in man are not severe and occur on dosage only on the upper limits required for efficient clinical effect.

These side-effects have been listed by Selikoff, Robitzek and Ornstein (1952)[182] as vertigo, constipation, twitching of the lower extremities, drowsiness, headache, hyper-reflexia, dryness of the mouth and delay of the urinary stream. Isoniazid acts rapidly and is very diffusable and satisfactory bacteriostatic levels in the cerebrospinal fluid are obtained easily on oral dosage (Fletcher (1953))[183]. Furthermore the drug has the advantage of being cheap and easy to produce.

So far, the only large scale properly conducted trials in its use have been reported in respect of pulmonary tuberculosis. These trials showed that if the drug was used alone bacterial resistance emerged[184,185] and therefore one had to employ also an adjuvant. Its use with P.A.S. was compared with streptomycin and P.A.S. and it was considered that both regimes were equally effective but isoniazid with intramuscular streptomycin gave superior results[71]. This impression has also been gained by Joiner et alia (1952)[186] and by Goulding and Robson (1952)[187] after experiments in mice. Singh and Mitchison (1954)[188] showed that streptomycin in high concentration exhibited a greater bacteriostatic effect than isoniazid in comparable concentrations and that streptomycin and isoniazid together had the greatest anti-tuberculous activity.

These series, so far reported, have all been related to the drug's use in pulmonary tuberculosis and therefore one awaits with great interest, in view of its promising results

so far in therapy, a controlled series in respect of tuberculous meningitis especially as its use with P.A.S. would obviate, to a great extent, the necessity for intrathecal therapy. It would still be necessary, of course, to carry out diagnostic lumbar punctures twice weekly for the first three weeks and thereafter weekly to assess progress in the C.S.F. and guard against complications.

Post-mortem studies by Ritchie, Taylor, and Dick (1953)[189] revealed that with streptomycin therapy the emphasis in healing lesions is one of regressive fibrosis whereas after isoniazid there is increased vascularity, absorption of caseation and diminution of epithelioid cells with resultant resolution even in old densely fibrosed lesions. They sounded a warning note, however, as four patients out of six who were treated with isoniazid and streptomycin showed areas of cerebral softening and haemorrhage and these patients suffered before death from fits which the authors related to swelling of tuberculomata.

However, the rapid action, lack of cumulative effect, and diffusibility would suggest from the evidence available that the best future therapy of tuberculous meningitis would be the oral administration of isoniazid with intramuscular streptomycin, diagnostic lumbar punctures and use of neurosurgery or intrathecal tuberculin in certain selected cases as indicated. The place now for para-aminosalicylic acid is more difficult to decide and there is a good argument for the use of isoniazid and P.A.S., thus requiring no

routine intramuscular or intrathecal therapeutic injections. Streptomycin is then kept in reserve for the deteriorating patient should bacterial resistance develop.

Isoniazid has been used intrathecally by Torres-Gost (1953)[63] in addition to oral dosage and intramuscular streptomycin. He describes the use of this regime in 100 cases and reports only 6 deaths but his follow-up period is too short for true evaluation. Other articles have reported the employment of isoniazid in tuberculous meningitis but are also difficult to assess correctly either because the numbers are too few[62,190,191] or the different groups (as so often happens) are not really comparable[60].

Recommended dosage is 8 - 10 mgms. per kilogram body weight per day given in two daily doses for the first week and then the dose is reduced to 7 mgms. per kilo. per day. In view of the success of smaller doses (3 - 4 mgms. per kilo. per day) in pulmonary tuberculosis it could well be that this dosage is too high. If vomiting does occur, the drug can be given by the intramuscular route.

Terramycin, Neomycin, Viomycin and Amithiazone

Three further antibiotics with an antituberculous effect are terramycin, neomycin[12,192] and viomycin but there are some dangers attached to their use.

The first one, terramycin, is given orally and does not appear to result in bacterial resistance[193] developing but its tuberculostatic effect is correspondingly less than that of streptomycin and it, therefore, has to be given in large

dosage (5 - 7 Gms.) which leads to a high incidence of gastrointestinal upset, anorexia being very frequent[194]. It can however be used as a substitute for P.A.S. and is extremely useful should sensitivity to the latter develop[193].

Neomycin and viomycin, on the other hand are potent agents but the former is excluded from use as an alternative or an an adjuvant agent to streptomycin because of its nephrotoxic and ototoxic effects[195,196]. The latter viomycin also causes a rather forbidding group of side effects - disturbances of the eighth nerve, the kidney and plasma electrolytes. It is possible that there will be a very limited indication for the use of this agent, in spite of it causing a high incidence of toxic reactions, in those cases where streptomycin resistance develops[193]. A dosage of 2 Gm. twice weekly may minimise the side effects and justify its use in place of the streptomycin.

Amithiazone is a synthetic drug that has been tried recently in pulmonary tuberculosis and 'found wanting' owing to an only moderate antituberculous effect, high toxicity and lack of prevention of the development of bacterial resistance to streptomycin when used in conjunction with the latter[193]. It need, therefore, not be considered further.

Using the analogy of a table presented by Crofton (1953)[197] for possible chemotherapeutic regimes in pulmonary tuberculosis we have, therefore, in respect of the present day treatment of tuberculous meningitis the following alternatives:-

1. Intrathecal and intramuscular streptomycin - of proved value especially if the regime is continuous at first and interrupted after the twelfth week.

2. Intrathecal and intramuscular streptomycin with the use of an oral adjuvant, preferably para-aminosalicylic acid - this is more effective than (1) and the danger of bacterial resistance developing is lessened especially with adult pulmonary phthisis complicating.

Alternatively to P.A.S. one of the sulphones could be used.

3. Oral isoniazid and intramuscular streptomycin - this regime is under trial, appears safe and promises to be the most effective and obviates intrathecal therapy. The only disadvantage is that the development of bacterial resistance may deprive the patient of both potent agents. The additional use of P.A.S. or a sulphone would probably be of no advantage.

4. Oral isoniazid and para-aminosalicylic acid - this treatment has two advantages in that no injection therapy need be given and streptomycin can be kept in reserve. Its use might therefore be reserved for children but often the disease is severe in the latter thus requiring the more effective combination of (3). Simple serous tuberculous meningitis is an obvious suitable indication for this form of oral therapy.

5. Terramycin and streptomycin or isoniazid - this could be a very effective combination. Terramycin, as the subsidiary

agent, need not be given in too large dose to cause gastrointestinal upset and might be tolerated better than P.A.S. Furthermore isoniazid or streptomycin would still be kept in reserve, but the latter would require to be given by combined routes.

Only further clinical trials of treatments 3, 4 and 5 with variation in details of dosage of the different constituents will help to decide which is the regime to favour.

Viomycin may have a very limited place as a last resort substitute for streptomycin.

However, in tuberculous meningitis one can dogmatically say that the following regimes are contraindicated:-

(a) Use of intramuscular streptomycin alone

(b) Para-aminosalicylic acid or sulphone alone

(c) Neomycin is too toxic and amithiazone ineffective

(d) Terramycin alone,- however may be useful substitute for P.A.S.

In addition one must not forget the employment of the other measures, neurosurgical, P.P.D. etc. and regarding each individual case,the management which has already been outlined above, and which still applies whatever specific chemotherapeutic routine is used.

Therapy of the future, therefore, promises to produce, along with the lessons of the past, continued improvement in survival rates.

CONCLUSIONS

Since the discovery of streptomycin by Waksman and his associates in 1942 the cure of many cases of tuberculous meningitis has become possible.

From an analysis of 52 cases treated by intrathecal and intramuscular streptomycin it was seen that one case in three survived, thus comparing favourably with the average survival rates of earlier series reported by other workers. However with increasing experience in management of the disease and use of adjuvant agents and neurosurgical methods the survival rates have improved so that now, just over one case in three did not survive.

It would seem that the form of therapy of proved value is intrathecal streptomycin of a dosage of 0.1 Gm. in 5 - 10 ccs. normal saline with reduced doses down to 0.05 Gm. proportional to age, given at midday, daily, for the first fourteen days and then three or three and a half times weekly up to the twelfth week. Thereafter intrathecal therapy is interrupted by rest periods and the frequency of injection gradually reduced and tailed off as the clinical condition permits. The intrathecal therapy should be at least 50% of the intramuscular and preferably about 75% for the first 12 weeks. Associated with the latter intramuscular streptomycin is given on a dosage 0.02 Gm. per pound body weight per day up to a maximum 1 - 2 Gms. (or 0.02 Gm. per kilogram per day) in a divided dose morning

and evening and should be continued for at least two months after cessation of intrathecal treatment with an average of six months total duration. The best type of streptomycin to use is the streptomycin sulphate.

Associated with the streptomycin an adjuvant is given and of promizole, promin, sulphetrone, thiosemicarbazone and para-aminosalicylic acid the latter named is best, as it is equally effective given orally and least toxic. Dosage should be 12 - 16 Gm. daily in three-hourly doses, preferably of the solution, given after meals when possible and with corresponding reductions for children according to age.

Should a block to the cerebrospinal fluid circulation develop with a communicating hydrocephalus intermittent ventricular drainage through frontal burr holes is indicated. Should the block develop with a non-communicating hydrocephalus streptomycin in reduced dose should be given intraventricularly concurrently with drainage and at the same time as lumbar route therapy. Should the block be in the spinal subarachnoid space and spontaneous clearing not occur readily intrathecal therapy will have to be continued by cisternal or ventricular route.

With deterioration in spite of these measures outlined above protein purified derivative of tuberculin given intrathecally in minute and increasing doses in the sensitised patient may then be tried to help resolution of the block.

Should bacterial resistance develop to the streptomycin, isoniazid in dosage 5 - 7 mgms. per kilogram per day in divided dose twice daily may be given orally in substitution for the streptomycin.

Supplementing these measures are a sanatorium type of light nutritious diet and regime with vitamins, iron therapy and intravenous fluids if required. Physiotherapy and occupational therapy are instituted as soon as the patient's condition permits and this will include re-education in walking and splinting of deformities under the direction of the orthopaedic specialist.

In the management of the disease important points are early diagnosis and in the difficult case to institute therapy without awaiting the necessary bacterial confirmation. At the onset of treatment, periodically during treatment, at the end of treatment, and in the follow-up, a full assessment of each case should be carried out including physical, radiological, bacteriological and ophthalmological examination. On admission a careful history and enquiry into possible tuberculous contacts is required. Initial, and in some cases serial, mantoux tests should always be performed.

Progress and prognosis are assessed at these regular examinations and is aided by the use of special temperature charts and graphs of the weight and of the behaviour of cerebrospinal fluid constituents. Favourable trends are falling temperature, weight rise, rising sugar and chloride levels and falling protein and cell count value in the C.S.F.

In this respect the most valuable constituent to watch is the behaviour of the cerebrospinal fluid sugar which is the first to return to normal, the protein being last.

Healing of choroidal tubercles and clearing of lesions in radiological pictures are favourable. Delay in diagnosis, age under 3 years, advanced disease on admission, marked neurosurgical signs and coma, tuberculosis elsewhere in the body, miliary disease, too early cessation of therapy, resistant organisms, hydrocephalus, tuberculous cerebral endarteritis, cerebrospinal fluid blocks and an innate weak resistance of the individual, are all unfavourable prognostic points.

In addition to the periodic full examination of the cerebrospinal fluid, estimation of cell count and protein value on each specimen after every lumbar puncture is necessary as a fall in the former and a rise in the latter will give early warning of a spinal subarachnoid block. Other signs (xanthochromia,+ve Queckenstedt test) will also be present and indicate the necessity for confirming the suspicion by use of the diffusion index. For bacteriological examination large samples of cerebrospinal fluid should be used.

Very careful follow-up with watch for signs of relapse or recrudescence after cessation of therapy must be carried out over the next few years and final results should not be assessed earlier than the two year period. The cessation of therapy should be decided after consideration of progress in all aspects over 2 - 3 weeks and during the follow-up period the routine examination as detailed above should be

supplemented by psychometric assessment and evaulation of hearing and vestibular function.

The agents streptokinase, A.C.T.H., heparin, potassium iodide, neomycin and amithiazone are not of value and viomycin is of limited use.

In the future it is likely that isoniazid will become the principle agent for use but until fully controlled trials have been carried out and reported the wisest course might be to keep this agent in reserve for the deteriorating case.

Isoniazid with P.A.S., isoniazid and terramycin, isoniazid with intramuscular streptomycin, and to a less extent terramycin with streptomycin by combined routes, are the regimes worthy of comparison with the older therapy of streptomycin and P.A.S. and of these newer groupings the evidence that is available would suggest that streptomycin and isoniazid as the most promising.

Whatever regime is employed, all accessory and neurosurgical measures, points in the management of the disease and frequent diagnostic lumbar punctures must not be neglected.

Prophylaxis of tuberculous meningitis by follow-up clinics of children suffering from primary complexes, by careful supervision of tuberculous contacts, by provision of a safe milk supply, by routine lumbar puncture in miliary tuberculosis, and B.C.G. vaccination should not be forgotten.

And so, whether the old or the new therapy is employed there is still required the nursing and medical care of specialised centres that have available the full resources of

a laboratory and wide range of specialist services. This latter, the newer chemotherapeutic weapons, and the management of the disease as outlined above, will give, in the near future, the case suffering from tuberculous meningitis at least 75% chance of survival, a dramatic and fast changing picture from that of ten years ago when death was almost certain. There will still remain those few cases whose disease is advanced on admission with the late effects of hydrocephalus and arteritis whose treatment will be intractable, and it is those cases that will form the stimulus to further advances in treatment and in prophylaxis.

Addendum: The use of a further new derivative of nicotinic acid, with antituberculous effect, has recently been described by McDermott, W. et alia in the Am. Rev. Tuberc. (1954), Vol. 69, No.3. He used this drug with isoniazid in pulmonary tuberculosis but although found to be a very effective combination, signs of liver damage in many patients have appeared. This may contraindicate its wider use in other forms of tuberculosis e.g. meningeal, unless future trials show reduction of dosage overcomes this toxic reaction without loss of clinical efficiency.

SUMMARY

An analysis of the results of treatment in 52 cases of tuberculous meningitis in which intrathecal and intramuscular streptomycin was used, is presented. These results are compared with those obtained by other workers and the variations in the different treatment schedules and the specific chemotherapeutic agents employed since the discovery of streptomycin are reviewed.

Opportunity is taken to discuss the different factors in diagnosis, prognosis, management, therapy, follow-up, pathogenesis and pathology of the disease.

Finally the newer antituberculous agents and possible future trends of therapy are briefly considered.

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Abreviations for journals and periodicals are as per Quarterly Cumulative Index Medicus.